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The Roosevelt
New York, N. Y., 18, 19, 20 October 1956

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1. Gross, J. M., Jl. Int. Coll. Surg., 23:24, '55.

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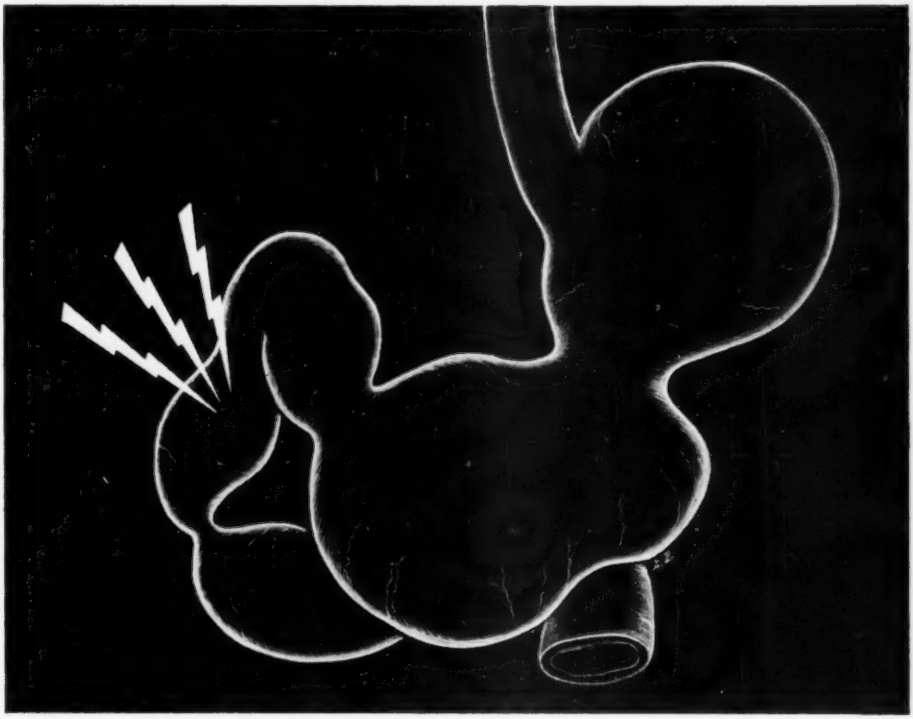

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1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

2. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E.C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

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1. Jacobson, P.: West. J. Surg. *63*:711 (Dec.) 1955.
2. Menger, H. C.: J.A.M.A. *159*:546 (Oct. 8) 1955.

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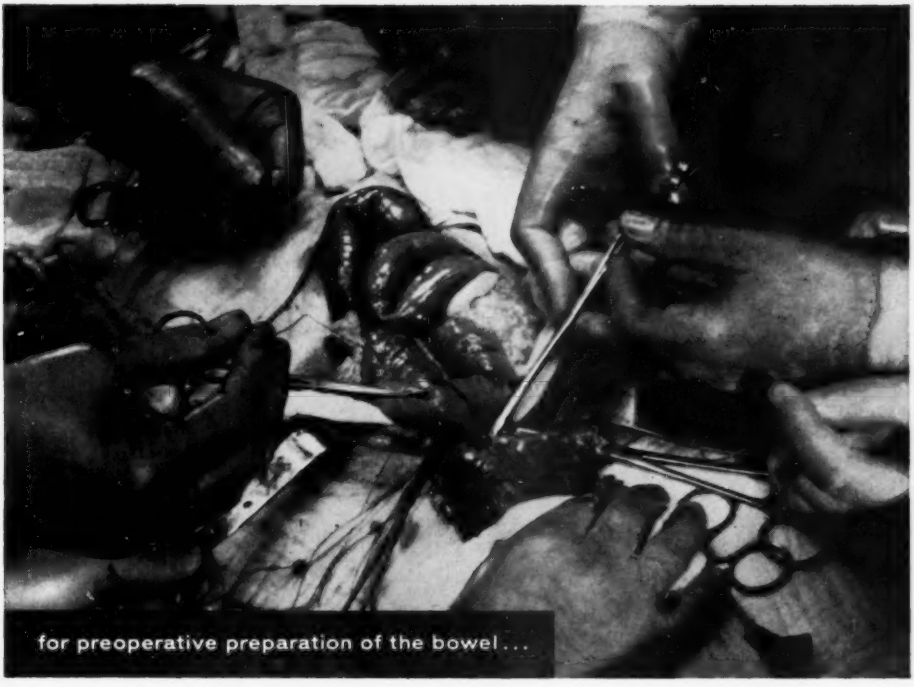

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1. Weiss, S. et al.: Amer. J. Gastroenterol. 24:523, Nov. 1955.

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1. Maynard, L.A., and Nelson, W.L., in Handbook of Nutrition, American Medical Association, ed. 2, Philadelphia, The Blakiston Company, 1951, p. 625.
2. Aughey, E., and Daniel, E.P., cited by Maynard, L.A., and Nelson, W.L.: Foods of Plant Origin, ibid.

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VOLUME 26 SEPTEMBER, 1956 NUMBER 3

PHYSIOLOGICAL AND CLINICAL OBSERVATIONS ON EXTRAHEPATIC BILE DUCTS*

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Quincy, Mass.

PHARMACODYNAMICS

The author first became interested in biliary dynamics in 1935 at the Mayo Clinic. This was the first time, to his knowledge, that pressure studies had been made on the common bile duct of a human[1]. A patient was studied who had a T-tube in the bile duct. She had been operated upon four times within a two-year period, and each time the T-tube was removed the pain reappeared in the form of acute biliary colic. Each time the T-tube was replaced in the bile duct by surgery, the pain disappeared. It was discovered that the biliary pain was associated with increased pressure in the bile duct. The increased pressure was found to be due to spasm at the lower end of the common bile duct. Since that time it has been the policy of the author to perform pressure studies on every patient who has a T-tube in the bile duct.

Two types of intrabiliary pressure are recorded: 1. The resting intrabiliary pressure and 2. the perfusion pain pressure. Intrabiliary pressure studies have served the following purposes: 1. indication as to when to remove the T-tube, 2. study of effect of drugs on the sphincter of Oddi, 3. study of residual biliary infection in the small radicles of the biliary tree.

The *resting intrabiliary pressure* is an index of the patency of the lower end of the common bile duct. On the average it is less than 30 mm. of water below the level of the ensiform process. Elevated resting pressures are due to: 1. spasm of the sphincter of Oddi, 2. edema of the ampulla of Vater, 3. pressure from an inflamed pancreas, or 4. a stone in the common bile duct. It was learned that spasm of the sphincter of Oddi can be produced by certain drugs, chiefly the opiate derivatives, morphine, demerol[3], codeine, pantopon and dilaudid[2]. The last being the least spasmogenic.

*Read before the Second Annual Convention of the American College of Gastroenterology, Chicago, Ill., 24, 25, 26 October 1955.

The spasm of the sphincter of Oddi was found to be relieved by nitroglycerin, amyl nitrite, and aminophyllin. It was found that the spasm of the sphincter of Oddi and spasm of the second portion of the duodenum are one and the same so far as the author's studies and reports are concerned[4].

The duodenal spasm secondary to morphine was found to occur, in spite of spinal anesthesia, up to the level of the second thoracic segment. A patient under spinal anesthesia developed biliary pain from duodenal spasm after morphine. The spasm was relaxed by amyl nitrite with relief of pain and drop in intrabiliary pressure (Fig. 1). These studies indicate that the mechanism of biliary spasm, therefore, travels through the vagus nerve, probably from the vomit center in the brain, and the pain fibers travel from the biliary tract toward the brain through the vagus nerve, rather than through the sympathetics.

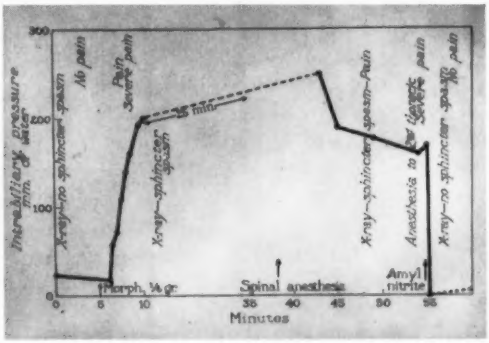


Fig. 1—This graph shows the intrabiliary pressure taken through a T-tube. Following subcutaneous injection of morphine sulfate there was an increase in intrabiliary pressure due to spasm of the sphincter of Oddi, as demonstrated by x-ray. Biliary pain occurred from increased intrabiliary pressure. Pain or spasm was not relieved by spinal anesthesia. Pain, spasm, and intrabiliary pressure were relieved by amyl nitrite.

The relaxing effect of amyl nitrite lasts 15 minutes, and that of nitroglycerin for one hour. Many times, however, by relaxing the sphincter of Oddi the relief of intrabiliary pressure results in permanent relief of pain, breaking a vicious cycle, and the spasm does not recur. The *perfusion pain pressure* is measured by running saline solution into the bile duct at gradually increasing pressures up to 550 mm. water. The pressure at which discomfort is noted is recorded as *perfusion pain pressure*.

The *perfusion pain pressure* is below 550 mm. water in 90 per cent of patients with T-tube drainage. Tolerance to perfusion pressure improves with T-tube drainage. The variation of pressure in the common bile duct and relation to pain is referred to as *biliary dynamics*.

Postoperative T-Tube Drainage

From these and other studies it was concluded that it is necessary to leave the T-tube in the common bile duct for drainage until the biliary dynamics are normal, that is, until all spasm at the lower end of the bile duct has disappeared and there is no evidence of sensitivity to perfusion pressure below 550 mm. water. The T-tube should be left in the bile duct, therefore, until the resting intrabiliary pressure is down to 30 mm. of water and the *perfusion pain pressure* is up to 550 mm. of water.

The value of a study of *biliary dynamics* is illustrated by the following case: In a previous communication a case was reported in which the patient had a stricture of the ampulla of Vater[5]. She was found at operation to be suffering from pancreatitis, as well as acute cholecystitis. Besides evidence of regurgitation of bile into the pancreatic duct, there was certain evidence that the pancreatic juice regurgitated into the biliary tree, producing inflammation in the small radicles of the biliary tree. Following cholecystectomy and T-tube drainage, the patient was symptom-free. With increased clamping of the T-tube, however, the chills and fever recurred. The T-tube was then left open continuously and signs of infection disappeared with further biliary drainage.

The lesson here is obvious and is that in this case, as in many others, the *residual biliary infection requires prolonged T-tube drainage of the bile duct and the T-tube should be left in until all signs of biliary infection have disappeared as indicated by normal biliary dynamics.* If the T-tube had been removed prematurely, symptoms would have recurred. Prolonged biliary drainage is necessary in many cases to prevent recurrences of biliary symptoms postoperatively. T-tube drainage has been carried out in many cases for three months and in some up to almost one year with no evidence of harm.

Biliary Dynamics

Resting intrabiliary pressure:—Pressure study is usually done three weeks after the operation. The resting pressure is generally elevated at first. The normal is less than 30 mm. water above the ensiform. Following the initial reading, amyl nitrite is given to determine whether or not the elevation is due to spasm or edema. If the pressure falls to normal following amyl nitrite, then one may assume that the elevation is due to spasm. The resting intrabiliary pressure is an index of the patency of the lower end of the bile duct. An elevated pressure may be due to spasm, ampulla edema, residual common duct stone, or pressure from edema of the pancreas.

Perfusion pain pressure:—Saline solution is perfused into the bile duct until the patient experiences pain. This is recorded as "perfusion pain pressure". If the biliary tree is free from infection, it will tolerate *perfusion pain*

pressure up to 550 mm. water. Many cases three weeks postoperatively have pain at perfusion pressures as low as 100 mm. water. Considerable evidence has been collected to show that perfusion intrabiliary pressure pain is an index of residual infection in the small radicles of the biliary tree.

Residual Biliary Infection

Fifty per cent of patients requiring cholecystectomy require common duct exploration and T-tube drainage. T-tubes should be left in as long as is necessary until *residual biliary infection* has disappeared. It was noted that the standard type of T-tube tended to be pulled out prematurely. It was considered advisable, therefore, to devise a type of T-tube which could not be readily pulled out accidentally. The author has used the McGowan-Keeley T-tube[6] consistently now for the past eight years. This tube is brought out through a stab wound to the right of the incision. The tube is superior to the conventional type in that the conventional tube tends to pull out and become "kinked" in the common bile duct, and finally it frequently becomes obstructed or is accidentally pulled out in its entirety.

In a recent review of a series of 25 cases of common duct drainage, the author was surprised to find that 30 per cent of these who had been jaundiced had evidence of extrinsic pressure on the bile duct as the cause of obstructions. One of these cases, previously reported, had developed acute infection in the radicles of the biliary tree while under T-tube drainage. There was a free flow of pus from the T-tube. Following injection of streptomycin into the T-tube, the bile became clear and evidence of infection disappeared in a matter of several days. Following this, the *perfusion pain pressure* improved remarkably. This is as one would expect, if one considers *perfusion pain pressure* as an index of *residual biliary infection.* More surprising, however, was the fact that the *resting intrabiliary pressure* also returned to normal in a few days. In other words, *as evidence of residual biliary infection subsided, the spasm at the lower end of the bile duct disappeared.* The inference from this observation is that the spasm at the lower end of the bile duct occurring in association with biliary pain is secondary to residual infection in the radicles of the biliary tree.

A study of the bacteriology of the bile from 30 cases with T-tube drainage tends to confirm the idea that perfusion pressure is associated with *residual biliary infection* and that spasm at the lower end of the bile duct is secondary to the infection in the biliary tree[8]. The study of 30 cases showed that 90 per cent of patients requiring T-tube drainage showed pathogenic culture from T-tube bile. The bacteria disappeared from the bile with prolonged T-tube drainage. The resting intrabiliary pressure tended to return to normal and the *perfusion pain pressure* improved as the bacteria disappeared from the bile. The use of streptomycin injected into the T-tube speeded the resolution

of *residual biliary infection* as measured by biliary dynamics and culture of bacteria in T-tube bile.

While the *residual biliary infection* tended to improve with T-tube drainage, streptomycin into the T-tube speeded the process of resolution.

Subsequent bacteriological study of the bile of 70 cases with T-tube drainage confirmed this finding[7] and showed also that terramycin acted beneficially in resolution of *residual biliary infection.*

Residual biliary infection was often found associated with obstruction of the lower end of the common bile duct due to spasm of the sphincter of Oddi or edema of the ampulla of Vater.

The nature and location of biliary pain brought on by perfusion of the ducts with saline was found to be identical with that suffered by the patient prior to surgery, and the same type and location of pain as is usually identified as being associated with cholecystitis. This and other studies pointed to the conclusion that biliary pain is usually due to pressure in an infected biliary tree and that the so-called *postcholecystotomy syndrome* or *biliary dyskinesia* is really a result of *residual biliary infection.* The residual biliary infection and associated spasm of the sphincter of Oddi disappear with prolonged T-tube drainage. The use of streptomycin injected into the T-tube or use of oral terramycin speeds up the process of resolution of postoperative *residual biliary infection.* This brings us to the next phase of our discussion, namely the use of choleretic agents.

A New Synthetic Choleretic

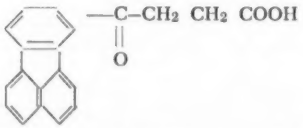
With good common duct drainage, one would think that any medication that would increase the volume of bile would be beneficial provided there was no obstruction in the flow of bile. In the presence of even mild biliary obstruction, however, any substance that would increase the volume of bile without lowering its viscosity or surface tension would simply add to the pressure in the biliary tree and work to the discomfort of the patient.

The agent that I am about to discuss, however, appears to have a unique quality in that it does seem to permit bile to flow more freely through a smaller opening and should be immeasurably beneficial in cases with partial biliary obstruction. This substance is Y-oxy-Y-fluoranthenebutyric, known as SC-1674.

A synthetic choleretic substance designated as SC-1674* was made available for study in May, 1952. It is a stable, golden yellow, crystalline solid, which is insoluble in water and acids, but moderately soluble in organic solvents and

*Synthesized and supplied by G. D. Searle and Company.

in alkaline media. The descriptive formula of SC-1674 is X-oxy-Y-fluoranthene-butyric acid and its structural formula may be represented as follows:



The oral LD_{50} of SC-1674 in mice is 1,160 mg. and in rats 2,500 mg. per kilogram of body weight. These ranges of toxicity indicate a high index of therapeutic safety.

SC-1674 was administered to a series of 25 patients who had T-tubes in the bile duct. The observations made from a study of the T-tube bile will be considered under the following headings: 1. change of color of bile from yellow to green, 2. solution of sediment, 3. detergent action, 4. lowering of freezing point, 5. apparent reduction of viscosity.

1. *Color change:*—The first thing noticed about the action of SC-1674 was that the bile changed in color from the usual canary yellow to a brilliant green. This indicates an improvement in liver function. The duct bile is usually canary yellow. It is only when the liver is in good condition when there is a rich store of glycogen that it excretes green bile directly into the common duct. The color change occurred consistently in every case studied.

2. *Sediment:*—The sediment was studied by centrifuging the bile and measuring the amount of sediment and studying the sediment microscopically. Sediment consisted of inspissated bilirubin, crystals, bacteria, occasionally pus and epithelial cells. Patients in whom sediment was found in the duct bile showed a rapid disappearance of sediment by the fifth day after daily administration of SC-1674. The quality of the bile definitely seemed to be improved. It changed from a muddy yellow appearance to a very transparent brilliant green.

3. *Detergent:*—There was also detergent action in the bile manifested by shaking the bile in the test tube. There was twice as much froth in the bile specimen after administration of the SC-1674 as before. The T-tube, after being removed from the common bile duct, was observed to be very clean, and free from sediment, whereas usually this tube is covered and plugged with encrustations of bilirubin. Even T-tubes left in several months were absolutely free from sediment. It has long been known that indwelling T-tubes or any form of prosthesis left in the bile duct inevitably become plugged with sediment. This feature of this choleretic, SC-1674, in keeping the indwelling tube clean and patent should prove very useful.

4. *Lowering of freezing point:*—The freezing point was lowered, indicating an increase of the ability of the bile containing SC-1674 to keep substances

in solution. Indications from these studies are that we are dealing with a stable bile acid preparation which by virtue of its stability in bile has an antibacterial action. This is brought about in two ways: a. by dissolving the sediment and leaving nothing for the bacteria to cling to, and b. the bactericidal action of the bile acids themselves.

5. *Viscosity:*—There appeared to be a lowering in viscosity. The bile seemed to flow more readily, although viscosity studies were not done from a scientific angle. If viscosity was lowered, one would expect that bile should flow through a smaller hole past a partial obstruction. This hypothesis was borne out by clinical experience in two cases.

In one of these cases there was an extrinsic obstruction to the common duct bile as a result of an inflamed retroduodenal lymph node proven in operation. The obstruction from this lymph node became worse postoperatively and finally was sufficiently severe so that it was impossible to clamp the T-tube off without causing the patient pain. The pressure required to force fluids past the obstruction was 290 mm. water. Following administration of SC-1674, the bile became clearer, the sediment disappeared, and the patient was able to clamp the tube for increasing intervals without pain, indicating the clearing up of infection and also that the bile was running through past the partial obstruction into the duodenum. Finally, after six weeks the patient was able to clamp the T-tube off all the time without pain. The resting intrabiliary pressure dropped from 290 mm. water to 50 mm. water in three weeks. This was more than a coincidental occurrence, since the patient had been three months without any evidence of improvement before administration of the choleretic agent. The biliary dynamics returned to normal and in due time the T-tube was removed. The patient has been in the best of health now for three full years.

The second case is that of a diabetic with partial obstruction from an edematous inflamed gallbladder which was so situated that removal was impossible. Moreover, the common duct could not be located because of the great degree of edema in and around the gallbladder. A mushroom catheter was put into the gallbladder for drainage. Postoperatively the mushroom catheter functioned for a short time only. On the second week postoperatively the bile ceased to flow from the tube in the gallbladder. The patient became deeply jaundiced and for a period of a month showed no evidence of improvement. There was evidence of impairment of liver function as indicated by a reversal of A/G ratio. The icteric index was 80. The patient was put on SC-1674. In a period of one month the jaundice had completely disappeared, the liver function returned to normal, and the patient has been asymptomatic for one year.

It is difficult to explain recovery of these two patients except on the basis that the preparation given changed the character of bile in such a way that bile was able to flow more readily past a partial obstruction. Improvement in

liver function and therefore body proteins led to ultimate resolution of the inflammatory process which had been producing extrinsic biliary obstruction.

We have, therefore, a preparation here which when taken orally will improve the quality of bile in a manner in which one would expect natural bile salts to do except more efficiently.

Clinical Application

The hydrocholeretic agent, SC-1674, should be considered worthy of trial in the following conditions: 1. *Postoperatively* in patients requiring T-tube drainage in order to speed up resolution of *residual biliary infection* in the smaller radicles of the biliary tree. 2. In cases of *postcholecystectomy syndrome,* which is really a *residual biliary infection* where the tube has been removed, or never was put in, and the patient continues to suffer following removal of the gallbladder. In these cases, the administration of the choleretic should be accompanied by the use of a. an antibiotic such as terramycin, followed by buttermilk, to restore intestinal bacteria, and b. the use of antispasmodic agents such as aminophyllin or nitroglycerin.

3. In cases of cholecystitis in which there is contraindication to surgery or in which the indication for surgery is not clearly defined, as in a normal functioning gallbladder.

4. In cases of *hepatocellular jaundice* where there is always a secondary factor of obstruction due to inspissated bilirubin in the bile canaliculae. Since this preparation appears to be without injury to the liver and probably beneficial to the liver cell, it should be given for trial in virus and serum hepatitis, since it should speed recovery of the jaundice by washing bilirubin out of the bile canaliculae. One patient with serum hepatitis was given this preparation with apparently excellent results.

5. In jaundice due to chlorpromazine or methyl testosterone, where the obstruction is in the bile canaliculae due to inspissated bilirubin, this preparation should prove a specific by dissolving the bilirubin in the cholangis.

6. Finally, with stricture of the bile duct, the preparation should be beneficial in washing out inspissated bilirubin.

7. In cases of reconstruction of the bile duct, where the use of T-tubes or over prosthesis is necessary, this preparation should be excellent in the sense that it prevents deposition of bilirubin. All the T-tubes removed from patients receiving this preparation were entirely free from any encrustations of any type and were perfectly clean.

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GLUTAMIC ACID IN HEPATIC COMA*

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The management of patients with hepatic coma is exceedingly difficult, and the ominous prognosis is indicated by the death of 38 out of 39 patients observed over a period of 4 years on the wards of Flower and Fifth Avenue and Metropolitan Hospitals. Similar results have been reported by Schwartz, et al[1] who reported the deaths of 20 out of 22 patients.

There is nothing specific about the biochemical abnormalities observed in hepatic coma. There is, however, some evidence pointing to disordered amino acid metabolism as a contributory factor in the pathogenesis of this syndrome. This particularly applies to glutamic acid metabolism in the various tissues, especially in the brain and spinal fluid, and the possible presence of methionine sulfoxide, which is a glutamic acid antimetabolite.

Glutamic acid is the only amino acid oxidized by the brain[2]. It is deaminated to alpha-ketoglutaric acid which enters the Krebs cycle, thus associating glutamic acid to carbohydrate metabolism. It can also bind ammonia to form glutamine, which is then metabolized without liberation of ammonia.

The blood ammonia concentration has been known to be related to liver failure for a long time. Bollman and Mann[3] showed in 1930 that there was a marked increase in blood ammonia concentration in hepatectomized dogs.

Fuld[4], in 1933, showed an increased blood ammonia in all diseases involving the liver, especially when urobilinogen was found to be positive.

In 1934, Mangnio and Krause[5] showed that Eck-fistula dogs which were fed large quantities of protein, frequently exhibited a comatose state associated with increased blood ammonia concentration.

More recently, Phillips et al[6] and Gabuzda et al[7], showed that ammonium cation resins, ammonium chloride, as well as increased dietary protein, all caused the syndrome of impending coma.

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Because of the important role that glutamic acid plays in both cerebral and hepatic metabolism, as well as its action upon the removal of excess ammonia, it was decided to try the effect of large doses of this amino acid in patients with either hepatic coma or impending coma. By coma, we refer simply to patients who do not respond to painful stimuli, have absent corneal reflexes and evidence of liver failure. By impending coma, we refer to those patients in liver failure who have a clouded sensorium and slurring speech, and are confused, drowsy, apathetic and disoriented.

Procedure

Our procedure consisted of the following:

1. An initial dose of 25 gm. of sodium glutamate was given intravenously, as an addition to 500 c.c. of 5 per cent glucose in distilled water.

2. If the patient failed to regain consciousness within a period of 4 to 6 hours, the first dose was repeated.

3. As soon as the patient regained consciousness, the intravenous glutamic acid (as sodium glutamate) was discontinued and 15 gm. of glutamic acid were given twice daily, either orally or by intragastric drip. This was continued until the mental status of the patient returned to normal.

4. The patient was placed on a low-protein, high carbohydrate diet.

5. The following biochemical determinations were made:

Total serum proteins	Alkaline phosphatase
Albumin/globulin ratio	Sedimentation rate
Total cholesterol/esters	Fasting blood sugar
Icteric index	Blood urea nitrogen
van den Bergh	Nonprotein nitrogen
Serum bilirubin	pH at 37.5° C.
Cephalin flocculation	Pyruvic acid in mg. per 100 ml.*
Thymol turbidity	Amino acid nitrogen in mg/100 ml.*
Prothrombin time/control	Ammonia in mcg. per 100 ml.*

Case Presentations

Six patients with hepatic coma were treated. Five were previously diagnosed as having cirrhosis of the liver, and the sixth was that of a viral hepatitis. We will summarize briefly the pertinent clinical findings, course, and laboratory data of these cases.

*Normal values: Ammonia 0-60 mcg. per 100 ml. whole blood (method of Conway) Pyruvic acid 0.9-1.1 mg. per 100 ml. whole blood (method of Friedemann & Haugen). Amino acid nitrogen 5-8 mg. per 100 ml. whole blood (method of Danielson and Frame, Russel, and Wilehlmann).

Case 1:—G. W., a 59-year old female with a 6-year history of cirrhosis of the liver, previously confirmed by biopsy, was admitted on September 26, 1954 to the Metropolitan Hospital. A four-week history of jaundice, dark urine, light stool and severe anorexia was elicited.

Examination revealed a mentally sluggish, white female who was confused as to time and place. There were numerous telangiectatic areas over the skin, which was markedly icteric. The liver was three finger-breadths below the costal margin and a flapping tremor of the wrist was present. Patient was given supportive therapy to which she seemed at first to respond. On October 13,

TABLE I

LABORATORY DATA (Case 1)

	9/27/54	10/11/54	11/11/54
Total proteins	6.6	5.5	4.9
Albumin	2.0	1.9	2.8
Globulin	4.6	3.6	2.1
Cholesterol	164	234	230
Cholesterol esters	21	75	60
Icteric index	83	54	61
van den Bergh	PDI	PDI	PDI
Cephalin flocculation	4 plus	4 plus	4 plus
Thymol turbidity	7.3	7.7	6.8
Prothrombin	25		
Alkaline phosphatase		5.1	
Urea nitrogen	13		
Blood sugar	75		

	10/14/54	10/22/54	10/25/54	10/29/54	11/3/54
pH	7.36	7.34	7.25	7.38	7.38
Pyruvic acid	2.25	2.38	2.19	1.91	1.80
Amino acid nitro.	15.1	14.8	13.6	12.9	12.0
Ammonia	390	370	310	260	230

1954, however, patient became disoriented, lethargic, and went into coma. Glutamic acid was instituted as above outlined, and two doses were given intravenously as sodium glutamate during the first 24 hours. Patient responded rapidly following the second dose and regained consciousness. Glutamic acid was then administered orally for eight more days. There was apparent improvement in the patient's physical and mental status and she was able to take nourishment by mouth. On October 15, 1954, patient vomited 500 c.c. of blood for which a Sengstaken tube was passed and kept in place for three days. After this episode, she continued to improve for the next six weeks when she became suddenly psychotic and had to be transferred to another institution.

Case 2:—H. C., a 66-year old female admitted to Metropolitan Hospital November 1, 1954, with a diagnosis of cirrhosis of the liver made at another institution. Chief complaints were shortness of breath and swelling of the abdomen and legs.

Physical examination revealed an obese, semistuporous, dyspneic, and deeply jaundiced patient who seemed confused, apathetic, and had a slurring speech. The abdomen was markedly enlarged with evidence of a fluid wave on percussion. After paracenthesis was done on the day of admission, the liver became palpable four fingers below the costal margin. Patient was given glutamic acid orally three times daily for four days. On the fifth day, the patient became alert and responsive, at which time glutamic acid was discontinued. On November 7th and 9th, patient had two episodes of hematemesis and expired after the second episode. Autopsy findings showed Laennec's cirrhosis with ruptured esophageal varices.

TABLE II

LABORATORY DATA (Case 2)

	11/3/54
Icteric index	43
van den Bergh	PDI
Cephalin flocculation	4 plus
Nonprotein nitrogen	30
CO_2 combining power	45
Blood sugar	94
pH	7.33
Pyruvic acid	1.95
Amino acid nitrogen	11.5
Ammonia	210

Case 3:—J. G., a 48-year old male admitted December 2, 1954, to the Metropolitan Hospital with a one-month history of lethargy, jaundice, and swelling of the abdomen and legs.

Examination revealed a lucid, markedly jaundiced patient. There were rales at both bases of lungs, free fluid in the abdomen, and presacral and bilateral leg edema. Because of possible heart failure, patient was treated with mercurials, ammonium chloride, digitalis, Vitamin B-complex and penicillin for one week. On December 9th, he lapsed into a deep coma. Glutamic acid was immediately instituted intravenously and the following day he responded sufficiently to be given glutamic acid orally. This was continued for four days after which he received "supportive liver therapy", including a high protein diet. During the following period of almost four weeks, patient remained mentally alert. On January 7, 1955, he again lapsed into coma. Intravenous glutamic acid was administered again, but patient died the same day after two episodes

of hematemesis. Autopsy findings showed Laennec's cirrhosis with ruptured esophageal varices.

Case 4:—H. G., a 42-year old male was admitted to Flower and Fifth Avenue Hospital on March 1, 1955, with complaints of jaundice and swollen ankles of one week duration.

Examination revealed an acutely ill, deeply jaundiced male with many *spider nevi* of the face and thorax. The liver was enlarged six fingers below the costal margin and there was pitting edema of both legs with tremors of both hands. On the day following admission, patient became restless, disoriented, confused, and developed slurring of speech. On March 3rd, sodium

TABLE III

LABORATORY DATA (Case 3)

	12/3/54	12/9/54
Total proteins	6.4	
Albumin	2.6	
Globulin	3.8	
Cholesterol	185	
Cholesterol esters	55	
Icteric index	81	
van den Bergh	PDI	
Cephalin flocculation	4 plus	
Thymol turbidity	1.1	
Pyruvic acid		2.21
Amino acid nitrogen		13.5
Ammonia		225

glutamate administered intravenously. Three hours after the first intravenous infusion, patient became aware of his surroundings, and his speech improved. He was subsequently placed on glutamic acid orally for four days. On March 8th, his sensorium was entirely clear, tremors of both hands were definitely diminished and patient was able to take nourishment by mouth. Three days later, on March 11, 1955, patient was found dead in bed.

Case 5:—D. S., a 60-year old female was diagnosed in December 1954 as having Laennec's cirrhosis. On March 14, 1955, she was admitted to Metropolitan Hospital because of weakness, swollen abdomen and failure to respond to her environment.

Examination revealed a thin, middle-aged woman who was jaundiced, stuporous and unable to respond to questions. The liver was palpable four fingers

below the costal margin. On March 15, intravenous glutamic acid was instituted and by evening patient appeared more alert and oriented to her surroundings. On March 16, patient was able to take nourishment. Unfortunately, patient expired on March 17, 1955.

Case 6:—S. T., a 15-year old white female was admitted to another institution with a two-month history of hepatic disease. On April 7, 1955, the patient developed diarrhea, jaundice and fever. After examination by a local physician, a diagnosis of viral hepatitis was made. Patient was put to bed for a period of

TABLE IV

LABORATORY DATA (Case 4)

	3/2/55	3/4/55	3/7/55
Total proteins	8.06	6.40	6.9
Albumin	3.65	3.10	3.6
Globulin	4.41	3.30	3.3
Cholesterol	352	272	176
Cholesterol esters	60	40	40
Icteric index	100	120	225
van den Bergh	DP	DP	DP
Cephalin flocculation	2 plus	2 plus	
Thymol turbidity	2	2	2
Alkaline phosphatase	48.9	33.5	21.2
Prothrombin	26.2	20	17.6
Urea nitrogen	11.0		
Blood sugar	89.7		
	3/4/55	3/8/55	3/10/55
pH	7.37	7.35	7.35
Pyruvic acid	2.19	2.10	1.82
Amino acid nitrogen	12.8	12.2	12.0
Ammonia	225	220	190

two weeks and became symptom-free. She was asymptomatic until June 4th, when jaundice reappeared and progressively increased in intensity. On June 8th, she was admitted to Bronx Hospital. On June 13th, she became stuporous, irritable, but was not out of contact with her environment. On June 15th, she became deeply comatose. Therapy had consisted of blood transfusions, ACTH, and antibiotics, but were of no avail. She deteriorated rapidly and on the 15th of June intravenous glutamic acid was given. There was no change in the comatose state, however, and the patient expired the following day.

Comment

Six cases of hepatic coma were treated with glutamic acid, both intravenously and orally. In all cases except that of viral hepatitis, the response was dramatic. In all cases except that of viral hepatitis, the episodes of coma terminated, the patients regained consciousness, and the mental state cleared up or improved sufficiently to permit nourishment by mouth and more intensive therapy for the underlying disease. Neither the underlying disease, nor the liver function tests, however, were affected by the therapy. In two cases, the levels of the ammonia and pyruvic acid were definitely lowered. The relationship of this decrease to the mental status of the patient is nevertheless difficult to evaluate. As previously stated, there is no specific correlation between the changes in the liver function tests and the development of coma[8]. The only persistent biochemical changes found by us were the high pyruvic acid and

TABLE V

Laboratory Data (Case 5)

	3/16/55
Total proteins	5.5
Albumin	2.4
Globulin	3.1
Icteric index	55
van den Bergh	PD
Cephalin flocculation	4 plus
Thymol turbidity	3.9
Urea nitrogen	35
Blood sugar	90
pH	7.39
Pyruvic acid	2.28
Amino acid nitrogen	13.7
Ammonia	240

ammonia values. The decrease in these values following glutamic acid therapy may have some significance. Amatazio and Nesbitt[9], in the study of 36 cases with liver disease, showed that the mean blood values were higher for pyruvic acid in patients with coma than in any other liver condition. That it was not due to anoxia was shown in a series of emphysema patients who had no elevation of pyruvic acid values. As to the ammonia elevation, the exact relationship of the persistent elevation of ammonia in blood or plasma to the state of consciousness, is hard to appraise. Schwartz and his co-workers[1] found that the blood ammonia values in severe liver disease were elevated with the range up to seven times that of normal. Their conclusion was that even though there was no consistent correlation between the degree of consciousness and the blood ammonia, still, the blood or plasma ammonia correlated better with the clinical status than any other available chemical determination.

The exact mechanism by which glutamic acid restores consciousness is not entirely understood. Its beneficial effect may be due to: 1. its ability to unite with ammonia to form glutamine which in turn is metabolized without the liberation of ammonia; or 2. its ability to combine with pyruvic acid and oxalacetic acid thus preventing ammonia formation. Whatever the mechanism, the fact remains that it does restore consciousness and improve the mental status of the patient, thus enabling one to proceed with more intensive therapy for the underlying disease. Any therapeutic agent which offers some hope in a clinical syndrome in which the prognosis is so ominous should be further evaluated. The beneficial effect of glutamic acid upon our cases of hepatic coma

TABLE VI

LABORATORY DATA (Case 6)

	6/10	6/11	6/13	6/14	6/15
Total proteins	6.2				
Albumin	3.5				
Globulin	2.7				
Cholesterol	124	137	104		111
Cholesterol esters	34	68	18		16
Icteric index	70				
van den Bergh	PDI				
Cephalin flocculation	2 plus				
Alkaline phosphatase			4.3		
Urea nitrogen	12		14		
Blood sugar	107				
pH				7.38	
Pyruvic acid				2.38	
Amino acid nitrogen				14.6	
Ammonia				340	

was similar to that of Walshe[10] who has treated five episodes of coma in three patients with subacute or chronic liver injury. On each occasion, the return to consciousness followed closely the administration of glutamic acid.

In view of our experiences and those of Walshe, we feel that further evaluation of the efficacy of glutamic acid and the mechanism by which it works is justified.

SUMMARY

1. Six patients with hepatic coma were treated with glutamic acid both intravenously and orally.

2. All cases except that of viral hepatitis regained consciousness within 18 hours.

3. The clearing of the mental state enabled the patients to take medication and nourishment by mouth.

4. Time was gained to treat the underlying disease.

5. Glutamic acid does not affect the course of the underlying disease nor the liver function tests.

6. In two cases, the blood ammonia and pyruvic acid levels were decreased.

7. Further evaluation of the use of glutamic acid in hepatic coma is warranted.

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Discussion

Question:—I want to ask the doctor, on the glutamic acid, how did he become aware of it in the first place as a method of treatment?

Dr. N. W. Chaikin:—The use of glutamic acid is based on its ability to remove an excess of ammonia from the various tissues; glutamic acid was used by Walsh in England successfully in five episodes of hepatic coma.

CLINICAL GUIDES TO DIAGNOSIS OF JAUNDICE*

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After looking over the program and noticing the subjects and the array of medical and surgical talent behind the subject material, I feel rather naive in approaching you, and with a certain element of temerity, to think I might add something to what has already been presented to you.

I think somewhere in my college courses one of the first things I learned was that the first law of logic is to define your terms. That is what we want to do this morning before we go into the subject matter.

I intend to confine my remarks entirely to the subject as stated. I consider myself an ordinary garden variety type of physician with a leaning toward internal medicine, and emphasize both to myself and my students, the approach to a diagnosis of a problem as much as possible at the bedside.

Ofttimes, the diagnosis, as Sir William Osler said, rests upon the clinical course of the disease. Also, as you know, as Osler said, get the patient's history. The history and the course of the disease sometimes resolve the diagnosis.

Now all of you here are old enough and have had enough experience with jaundice, I am sure, to appreciate the problem that you have at the bedside.

Today, in considering the clinical guides to the diagnosis of jaundice, I am going to confine my remarks strictly to a consideration of the problem. Is it a medical or a surgical problem, discounting, if you will, the hemolytic types of jaundice which I do not think are too difficult to diagnose, if given a little time and consideration.

So, over a period of years, all of us, sooner or later, evolve a pattern of approaching a problem. In the time I have been in practice, I have evolved a pattern that I use in approaching a case of jaundice, whether it is medical or surgical, and I offer it to you for your consideration. You may have methods that certainly are more superior than mine. You may employ various liver profile tests I have never heard of and, in your opinion, are better, i.e., in your hands have had the best results. So, I am offering my particular method of approach.

Ofttimes, the diagnosis of a disease can be made on one single thing. It is not unusual, I am sure, for any of us to pick up the telephone and hear an excited voice on the other end telling you, "My 18-year old daughter was watching television; had a bursting headache; fell to the floor unconscious; and has

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a stiff neck." By and large, and I think Dr. Snapper will agree with me, that is a ruptured basilar vascular artery aneurysm with subarachnoid hemorrhage.

Or there is the man who tells you he has a tearing sensation across his chest, and it goes up either to his neck or shoulders. By and large, that is an acute coronary occlusion with infarction, or it might be a dissecting aneurysm. It might also be an aneurysm eroding the cervical spine.

So, with these few considerations, what do I, as an individual do when I see a case of jaundice? Like everyone else, I revert to certain standard stereotype methods of approach to a diagnosis viz:

1. I play the percentages. What is the percentage of incidence, generally, for a particular type of jaundice?

2. What is the percentage of probable incidence in certain age groups?

3. Certainly not to be neglected, is the history—e.g. tunnel diggers, sandhogs with chills, fever, sweat, jaundice, think of Weil's disease.

4. Symptoms and physical findings.

5. Certain routine laboratory studies, and then special laboratory studies, viz, the so-called liver profile tests.

Lastly, other procedures, if no diagnosis is made.

Now, Portis[1] quoting Lichman here some time ago, who analyzed something like 1,000 cases of jaundice, divided them as follows: 50 per cent fell into the medical category and 50 per cent, more or less, fell into the surgical category.

Ten per cent of the 50 per cent of the medical category were hemolytic, and the remaining 40 per cent were septic, chemical, or infectious types of jaundice. In the surgical, half and half were benign or malignant conditions.

Now we are not, as I say, going to discuss the physiology and secretion of bile and anatomy and functions of the liver, just my particular approach to the diagnosis of jaundice.

Let us take you by the hand, so to speak, to the bedside of a patient with jaundice and see what thought processes go through my mind in trying to resolve the situation.

We are not going to discuss, of course, whether it is jaundice or not jaundice, e.g., whether it is carotenemia. We take for granted that, sooner or later, you know what a case of jaundice is at the bedside, and especially in good daylight.

(Slide) This is a slide taken from Schiff[2], in an analysis of 575 cases of jaundice. It is from the Cincinnati General Hospital, seen on medical and sur-

gical services. These are unselected. You see the hepatogenous group is 65 per cent; neoplastic group 21 per cent; calculous, which might be surprising to you, 6 per cent (at least in these figures), and undetermined 4½ per cent; miscellaneous 3.5 per cent. That is the breakdown of these 575 cases. These figures are from sometime ago, so maybe the situation has changed.

(Slide) Now from the same analysis, with a little more specific breakdown, indicating the relative incidence of various types of jaundice in 245 patients, 40 years of age or more. Here you begin to see more or less categorically they are classed more specifically.

Here neoplastic assumes, in his figures, 42.6 per cent; hepatogenous 38.9 per cent; calculous, 14 per cent; undetermined, 2.5; and miscellaneous, 2 per cent. You begin to think in the middle age or older group of two things, viz, primarily neoplastic or hepatogenous. So, that is what goes through our minds as we think of the probable percentage incidence of a particular type jaundice.

Before we go to the next slide, which we will review again, and the last slide, you understand we are discussing the medical, namely, hepatogenous type of jaundice in contrast to the obstructive which usually results in a surgical therapy. Therefore, the diagnosis is most important. Overlapping does occur and I am thinking of the profile test of obstructive and hepatogenous. You can have obstructive features in a purely intrahepatic type of disease, viz, very severe hepatitis with intrahepatic obstruction. Steigmann[3] and Popper have brought this out. You can have what starts purely as obstructive jaundice and then get an ascending involvement of the liver and therefore have an associated hepatitis.

So, it certainly makes it very difficult at times, especially if the cases are protracted, to make the differential diagnosis, particularly if you rely on the so-called liver profile test alone.

(Slide) Now, I am at the bedside. If I have a patient in the age group of child to a young adult, I think of something like this: First, hepatitis, acute hepatitis, very common, i.e., viral hepatitis, I think, too, today, with the frequency of transfusions and inoculations, etc., of homologous serum jaundice. Less likely but possibly I think of such things as infectious mononucleosis, blood dyscrasia, sepsis, toxins, chemical, and so on. Rarely is it present in a child but, certainly it occurs, obstructive, either from stones or adhesions or congenital defects.

Then, too, there is the so-called Gilbert's disease, or constitutional hyperbilirubinemia, for the most part seen in young people. In this condition the liver has a brown pigmentation. Histologically, if I remember, it is normal. It is a rather innocuous situation, and not incompatible with life. Thus when I see a young person, i.e., from a youngster to adult age, that is what goes through my mind on the possibility of percentages.

(Slide) Now with a young adult to middle age, I do not think I am playing my percentages too close here if I think along these lines:

First, hepatitis, either acute, viral or homologous serum jaundice. Hepatitis, again, but acute recurrent, such as seen in a person with cirrhosis of the liver.

Then further down I think of a common duct stone and, lastly, obstructive jaundice, extrahepatic, due to extrinsic pressure, such as neoplastic invasion.

As I say, this is my 2x4-brain method of going at it. You may think entirely differently, and justifiably so, in your particular type of experience.

(Slide) In middle age to old age, I think differently now. I think first of obstructive jaundice, either extrahepatic, such as carcinoma of the head of the pancreas, carcinoma of the ampulla of Vater or common duct stone. I think of a metastatic affair to the liver. Then possibilities in male or female kind of change my approach too. In the female I lean more probably toward a stone. In the male I probably lean more toward carcinoma. You may think I am shaving it pretty thin. Maybe I am, but that is the way I am impressed.

Further down the line, and less likely, I am beginning to think of hepatitis, viral or homologous serum jaundice. Maybe I should consider it a little more strongly in view of the widespread use of blood and plasma.

Apropos of that, there comes to my mind an old man in his seventies, in his late seventies, with what appeared to be a silent jaundice, relatively progressive, but he was in good spirit. There was not a significant weight loss but, playing my percentage, I thought first and foremost of carcinoma of the head of the pancreas.

As I went to his bedside and as I talked to the individual, and as further studies showed, he told me that he was, I think, in Michigan and he was in an automobile accident two or three months ago. He received plasma and blood transfusions. Take my word for it, to make a long story short, it turned out to be homologous serum jaundice—the exception that proved the rule.

Hepatitis recurrent, I always think of cirrhosis of the liver because these people have bouts of hepatitis, with or without jaundice. I still see it in middle age and old age.

Way down the line, sepsis, blood dyscrasias, toxins—thorazine and methyl testosterone today may be productive of jaundice, especially, I suppose, in old age. In old age, if I see somebody in jaundice and he is in a geriatric institute and a little disturbed and has been taking thorazine, perhaps it is due to the thorazine.

As I say, that is my approach, predicated on the age of the individual who comes to us with his problem of jaundice.

(Slide) Now, the history. Get the patient's history; get the patient's story.

The occupation of the individual may enter into it, as we mentioned before in our opening remarks, such as Weil's disease. Laboratory workers, and those in other occupations may be exposed to innocuous chemicals, producing hepatitis due to chemical insult to the liver parenchyma.

In the female, I think along the line of gallbladder disease with a stone.

Again, in developing the story, what about the onset of this thing? Was it sudden? Was it slow?

The incubation period of homologous serum jaundice as against viral hepatitis is a little bit different. It is more prolonged usually in the homologous serum jaundice and shorter in viral hepatitis.

Previous history: You may solve your problem immediately. "Yes, Doctor, I have gallstones, and I have had jaundice before." It certainly is not an unreasonable assumption, therefore, to think this present jaundice is due to the same thing. After you think that way, you open it up and find she has a carcinoma of the biliary tract.

Symptoms: By and large, I think once jaundice develops, invariably, depending upon its intensity, symptoms are pretty much the same, with a few exceptions. Rather marked jaundice, obstructive in nature, with pruritus attending it might be more severe.

Severe, overwhelming viral hepatitis, with marked destruction of the liver parenchyma, may have coma, or you know it is viral hepatitis and you are a little bit too zealous with your protein therapy and may possibly induce coma. So the picture changes, too. Or in cirrhosis of the liver, with ascites, edema, you may push ammonium chloride, and again induce the hepatic coma. Whether or not glutamic acid is always effective, I do not know.

So, by and large, I do not think there are symptomatic manifestations other than perhaps pruritus, coma, pain. Pain I would certainly associate with stone, possibly with neoplasm, not usually with hepatitis.

Overwhelming toxemia is more viral, again, rather than obstructive. Symptomatically, I am not helped too much.

(Slide) Now the value of the physical findings varies with recurrent hepatitis, such as seen in cirrhosis of the liver, not always, but there are certain features that are helpful to you. The thin hair in the male, the hypogonadal features, the delicate skin texture, alopecia, spider telangiectasia; and the liver, depending upon whether you see it in the hypertrophic or atrophic stage, hard, irregular, large or small and atrophic.

In acute hepatitis, as a rule, the liver is enlarged, smooth and tender, and in overwhelming viral hepatitis, with a production of either acute yellow or

acute red atrophy, the liver shrinks down and is small. If that is present, usually you have a very ill patient. If it is due to gallbladder with stones, physical findings may reveal localized right upper quadrant tenderness and rigidity, not necessarily associated with liver enlargement.

Carcinoma of the head of the pancreas or the biliary passages or the ampulla of Vater, with obstruction to the duct, produces the large, palpable gallbladder, the so-called Courvoisier's law. I do not know how many people believe in that so much but those are some of the things that come to my mind.

If the liver is enlarged and it is irregular, and I have no cause to suspect cirrhosis of the liver, then I think, in a backward manner, of a possible metastatic lesion to the liver, and the primary source, may not, at the bedside, be obvious. You have all seen bronchiogenic carcinoma with involvement of the spinal cord which may be the first manifestation; or not infrequently, small, anaplastic carcinoma of the stomach may hit the liver.

So, if I have no evidence of other pathologic involvement, cirrhosis of the liver, and I have a patient with jaundice, the liver is enlarged and irregular, then I am justified in thinking: No. 1, metastatic carcinoma of the liver; No. 2, possibly, primary carcinoma of liver.

Just to make the cheese more binding, as they say, not unusually your patient with cirrhosis of the liver will have an associated primary carcinoma. I do not know what the incidence of that is. In different places that I have been, the percentage is small, 1 to 5 per cent. Other people may have different experiences. The fact of the matter is, it does occur.

If I might digress here, I was going to discuss treatment. If you thought you had cirrhosis of the liver all the time and things are not going as they should, and I have had this experience, you resort to needle biopsy, and then may pick up the carcinoma. Certainly that category places your man in a different position.

Well, now, supposing you have jaundice. There is no enlarged liver, no particular skin manifestations, but enlarged superficial glands, cervical glands, or elsewhere. You think of Hodgkin's, lymphosarcoma with liver invasion. That is going down into the barrel a little bit, but it happens.

(Slide) Now the value of the routine laboratory test. You may do certain routine laboratory tests without resorting to extensive so-called liver profile studies. Ordinary blood count might reveal that you have infectious mononucleosis with jaundice as a manifestation, or possibly leukemia.

Watson[4] and others have stressed that if you have urobilinogen in the urine, in good amounts, you certainly lean more toward hepatitis rather than obstructive type of jaundice. If you definitely do not have any, you are thinking more, certainly, of obstructive jaundice. I put this as routine laboratory test because

some of these things in certain hospitals are absolutely routine, particularly x-ray of the chest. In routine x-ray of the chest, if you see glands or what might be bronchogenic carcinoma, then there is your clue, without necessarily resorting to a lot of liver profile tests.

I always get a flat plate of the abdomen as routine. In people with jaundice, I do not think gallbladder visualization is too informative. If I have a patient with jaundice and I am puzzled, I get a flat plate, and if it reveals a radioopaque shadow in the gallbladder, think rather of a calcified calculous rather than a cholesterol stone.

Serology: I do not know whether luetic hepatitis is passing out of the picture with present-day therapy. I hate to think we will be lulled into a sense of false security thinking that syphilis is entirely gone. But I still think, again, in some of these things too, if serology is positive or doubtful, you may think in terms of lues, but you may have other things which we mentioned previously, like infectious mononucleosis, which may give you a false positive.

I want to mention in passing, if you have the positive serology and you are puzzled, maybe the so-called T.P.I. test is more reliable, when you have a case of doubtful serology—viz. Treponema immobilization test.

(Slide) Maybe Dr. Snapper and Dr. Wagensteen use entirely different tests or more tests and cancel out some of these, I don't know, but this is what I usually start with, and I am not being smug, by any manner of means. You can have overlapping features of obstructive and hepatogenous type of jaundice in the same individual, particularly apropos, your liver profile.

If I see an immediate, direct van den Bergh, if I see a gradually rising icterus index, with or without reaching a plateau and staying there, and with 1 or 2+ cholesterol flocculation, or negative cholesterol flocculation and a normal thymol turbidity, or an increase above 10 of the alkaline serum phosphatase, and getting daily urine bile and urobilinogen and the urobilinogen is either nil or in small amounts or entirely absent, but bile is present, think of obstructive jaundice. Dr. Watson particularly emphasizes that if you have fecal urobilinogen of 5 mg. or less, he considers that complete obstruction jaundice.

The prothrombin time, in a way, will help you toward differentiating obstructive or hepatogenous, also you want to know whether or not you are going to do a liver biopsy. In obstructive jaundice, the bile cannot get in so there is depression of the absorption of the fat soluble Vitamin K. If you give those people Vitamin K, the prothrombin time changes, but the same is not true very often for the hepatogenous type of jaundice.

If I have an indirect, delayed van den Bergh; icterus index, which is gradually rising, there is the clinical course of the disease, and then reaches a plateau and stays there, and then comes down, that fits in with hepatitis. The cephalin cholesterol flocculation is always positive, usually 4+, and you want that in

24 to 48 hours. Thymol turbidity is markedly increased. The alkaline serum phosphatase is normal, or slightly increased. You have adequate quantities of urobilinogen in addition to bile. The total serum protein is always affected, particularly the total bile in the stool may be way below normal, but above the minimum figure that Dr. Watson adheres to.

(Slide) Now if I have racked my brain, talked to my patient and watched the clinical course and I still haven't arrived at the diagnosis, then I think these three things are indicated: Liver biopsy, which I shall only mention in passing because I notice in the program that someone is discussing it. Peritoneoscopy, perhaps I should touch that. If you are surgically minded, you are going to open them up and take a good look. Maybe I should skip peritoneoscopy. Surgical exploration, certainly, after due course and consideration, before your patient is in too poor nutritional state, should be considered.

The first article in last week's J.A.M.A.[5] is a surgical treatment, particularly common duct drainage, in cases of hepatitis, subacute or chronic. You have all had enough experience with these cases to know that they are not as clean cut as you would like to have them.

Not too long ago, I had a dear doctor friend of mine whom I insisted had viral hepatitis. His jaundice was severe. It was months before he entirely cleared up.

In case of doubt, with the present-day surgical technic, antibiotics, M.D. anesthetist, one is not too far wrong to induce surgical exploration.

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EXPERIENCES WITH NEEDLE BIOPSY OF THE LIVER*

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INTRODUCTION

In recent years needle biopsy of the liver has assumed importance in the diagnosis of liver disease. It has been proven to be a relatively safe investigative procedure in understanding the various diseases of the liver, many of which previously had required either surgical or autopsy confirmation[2,7,12,15,17]. Because of the relative ease of performance and the emphasis which physicians place on a histological diagnosis, the procedure has become almost universally

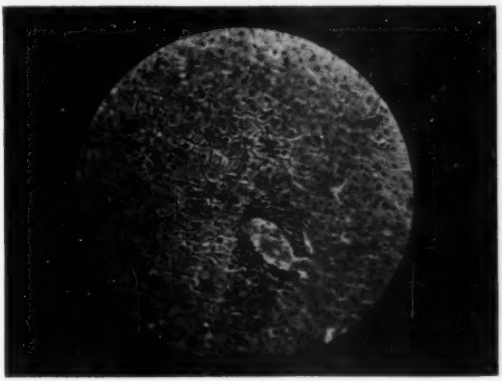

Fig. 1—Normal liver in 25-year old medical student with congenital hyperbilirubinemia.

accepted as one of the most accurate methods of diagnosis of liver disease. This has been especially true with serial biopsies[18]. In our experience, however, the pathological diagnosis obtained, in many cases, did not correlate with the final clinical diagnosis, or particularly correspond to experiences reported in the literature by other investigators[2,5,7,13,16,17,19-22]. The diagnostic accuracy for establishing a diagnosis has been reported to vary from 22 to 49 per cent; for

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confirming a clinical impression to vary from 24 to 59 per cent; and for not being of any diagnostic value to vary from 20 to 26 per cent[18,1,2,5]. Consequently, we have reviewed a series of consecutive liver biopsies in an attempt to determine the diagnostic accuracy and morbidity, in a hospital in which this procedure has not been emphasized. This would simulate conditions in most general hospitals.

Material and Methods

This is a report of 100 consecutive needle biopsies of the liver on 81 patients at The Ohio State University Medical Center done by or under the direct supervision of a staff member. Because it is felt that some error in interpretation may result in comparing the pathological diagnosis to the initial clinical impression (since in most publications it is not stated whether this impression is that of intern or staff), the pathological diagnosis was compared to the final diagnosis that appeared on the chart. The final diagnosis was obtained by autopsy, exploration, or the clinical course of the disease. Patients have been followed for as long as four years.

TABLE I

Diagnostic Value of Liver Biopsy

	No.	%
Biopsy established diagnosis	16	16
Biopsy confirmed clinical diagnosis	34	34
Biopsy not diagnostic	50	50
Total	100	100

The indications, precautions and technic for needle biopsy of the liver were followed as reported in the literature[3,4,6-8,12,13,16]. A Vim-Silverman needle was used and proved to be very satisfactory. Prothrombin time and bleeding and coagulation times were checked in all cases. Great care was taken to properly position and anesthetize the patient. The specimen was fixed in 10 per cent Formalin and sent, together with a short clinical history, to The Department of Pathology. It was studied with other surgical specimens with no particular emphasis being placed on this tissue. It is felt that this simulates conditions as found in most general hospitals throughout the country and would help to evaluate this procedure for general usage rather than that limited to teaching hospitals where needle biopsies of the liver are emphasized.

Results

Table I shows our analysis of the diagnostic value of needle biopsy of the liver. It will be noted that the biopsy definitely established a final diagnosis

in 16 per cent of the cases, confirmed the final clinical diagnosis in 34 per cent of the cases, and was not diagnostic or provided no assistance in the management of the patient in 50 per cent of the cases studied. The latter group included 21 cases in which biopsy was unsuccessful for reasons listed in Table II, including 29 patients in whom the needle biopsy revealed normal liver. Table II shows

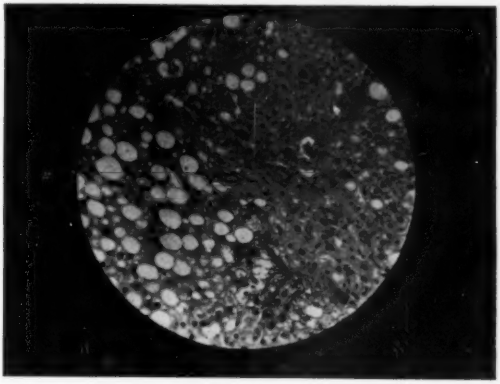

Fig. 2—Marked fatty infiltration.

an analysis of the 21 cases in whom the biopsy was considered unsuccessful for diagnosis. These figures are self-explanatory.

Table III indicated the diagnostic accuracy of the needle biopsy in some of the major types of liver disease which commonly cause confusion in diagnosis. It will be noted that metastatic carcinoma was confirmed in 15 of 23 patients

TABLE II

Unsuccessful Biopsies

1. Inadequate liver tissue	7
2. Laboratory accidents	4
3. Other tissue	5
4. No tissue obtained	2
5. Patient reaction	3
Total	21

or 65 per cent; that it confirmed the diagnosis of cirrhosis and cholangitis in a significant number of cases; that the biopsy was of no help in the lymphoma group.

Surprisingly enough, biopsy was of very little assistance in the diagnosis of hepatitis, being diagnostic in 43 per cent of the cases. The fact that this

latter group was frequently called cirrhosis in many patients in whom the clinical course definitely established a diagnosis of a viral type of hepatitis might account for the low percentage.

Of the 100 biopsies analyzed for this report, two patients bled to a significant degree. One required laporatomy for suturing of the biopsy site, while the other stopped bleeding spontaneously and did not require transfusion. Two patients developed the so-called phenomenon of "pleural shock"[7] and one patient developed a mild bile peritonitis. There were no other major complications although several patients did note transient right upper quadrant or right shoulder pain following this procedure. There was no mortality.

Comment

Any diagnostic procedure which potentially carries a significant degree of morbidity or mortality should be carefully evaluated as to its usefulness in

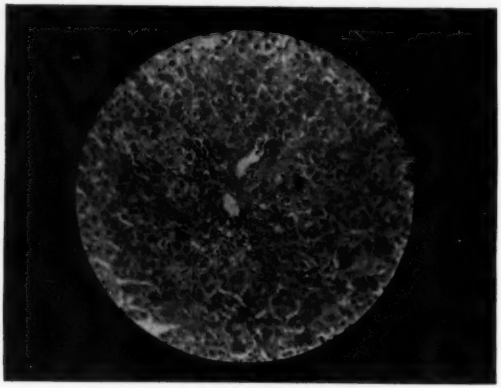

Fig. 3—Acute viral hepatitis.

diagnosis from the standpoint of its use in a general hospital and not in a specialized research organization. This evaluation should be approached from the viewpoint of safety and diagnostic accuracy. Reports from the literature as to mortality vary from 0.0 per cent to 1 per cent[5]. Terry, in a review of the literature totaling 10,600 cases, reports an over-all mortality rate of 0.12 per cent or about 1 per 1,000[15]. Zamcheck, in reviewing 20,016 cases reports a similar mortality of less than 1 to 1,000[21,22]. Morbidity has likewise been reported to be minimal[2,5,7,12,13,15,17,21,22]. This points to the fact that the technic should be carried out by someone thoroughly trained in performing this procedure and should not be done in a haphazard fashion by anyone mildly curious about liver disease[3,21,22].

In order to assure the maximum usefulness of this procedure, the complete and enthusiastic cooperation of The Department of Pathology is a necessity and the value of the procedure is in direct proportion to the interest of the patholo-

gists[3]. This varies a great deal among hospitals and is proportionate to the number of procedures performed. Lack of uniform classification and terminology in histological liver disease can further complicate the picture[5].

From the data presented, it appears that this procedure is of little or no benefit in the diagnosis of the various lymphomata. It seems to be a useful procedure in the diagnosis of cirrhosis, cholangitis, hepatitis, and in proving the diagnosis of metastatic carcinoma. It has undoubtedly saved many individuals with carcinoma from a laparotomy to confirm the diagnosis. This is also true with hepatitis. A negative biopsy for carcinoma, however, by no means excludes the possibility of a metastatic neoplasm. One must realize that metastatic carcinoma and other diseases of the liver may exist simultaneously and that the punch may have missed a metastatic nodule[11]. This procedure is not

TABLE III

Diagnostic Accuracy

Proven Diagnosis	Attempted	Confirmed
Metastatic carcinoma	23	15
Lymphoma	6	0
Cirrhosis	25	19
Hepatitis	14	6
Cholangitis	3	3

a substitute for a laparotomy and careful surgical exploration in many cases where indicated or where the diagnosis is obscure.

Needle biopsy of the liver should probably take its place as the most accurate of our liver function studies. Since, however, its interpretation is varied by the factors previously discussed, the results should be considered in the light of the total investigation of the patient. Morphologic changes have never been completely or accurately correlated with the complex physiological changes in liver disease[1,2,7,9,10,14]. While there is no doubt as to the value of the liver biopsy as a diagnostic tool, it is no panacea in the diagnosis of liver disease and its indiscriminate use may lead one into diagnostic pitfalls. We feel that it carries a distinct hazard to the patient and increases the diagnostic accuracy by a significant but rather small percentage. The fact that the procedure is "helpful" and confirms a clinical impression which may be obtained by other safer laboratory means may not be sufficient reason to subject a patient to the mortality or morbidity, no matter how small. At the present time, its chief usefulness lies in the further elucidation of alterations in the physiology, anatomy, and the pathology of liver disease.

Summary and Conclusions

1. The diagnostic value of 100 consecutive liver biopsies performed at The Ohio State University Hospital is reported.

2. The anatomical diagnosis is compared to the final clinical diagnosis. It is shown that the biopsy established a diagnosis in 34 per cent of the cases, and provided little or no diagnostic help in 50 per cent of the cases.

3. Morbidity and mortality of the procedure are presented.

4. The place of the liver biopsy in the over-all diagnosis and management of the patient with liver disease, is discussed.

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Discussion

Dr. I. Snapper:—Dr. DeFeo and I come from the same stable, the Cook County Hospital; therefore, in many ways we think the same. I cannot, however, agree with playing percentages for diagnostic purposes. It seems unwise to me to apply these parimutual methods in medicine.

For the differential diagnosis between obstructive jaundice and hepatitis, pruritus does not help too much. In general patients with obstructive jaundice have more pruritus than patients with hepatitis. It is certain, however, that patients with hepatitis may have pruritus and patients with destructive jaundice may not have pruritus. Noncomplicated hemolytic jaundice, of course, never causes pruritus.

The presence of gallstones on the x-ray or the history of previous gallstones is certainly a point in favor of gallstone jaundice. The presence of gallstones, however, is no insurance against hepatitis. Many patients who have gallstones as elicited by a flat plate of the abdomen, suffer at the same time from jaundice due to hepatitis, the latter proven by liver tests and liver puncture. Even when the correct diagnosis of these two coincidental diseases has been made, the patient is usually operated. Then gallstones are found but the common duct is normal and not dilated. This proves that the gallstones did not cause the jaundice but that the gallstone patient suffered from a hepatitis.

I am in favor of operating ulcer of the duodenum when necessary, but if possible not during an acute hemorrhage. Just so am I in favor of operating gallstones, but not during an acute hepatitis. In these cases it is better to wait.

Dr. DeFeo asked, "What about Courvoisier's law?" We must realize that no laws exist in medicine; there are, however, rules and regulations. And with this restriction Courvoisier's rule is just as good today as 60 years ago when it was introduced.

Courvoisier said, "If the patient has deep jaundice and a palpable gallbladder, then the jaundice is probably not due to gallstones, but to a carcinoma of the head of the pancreas." We now can add,—"or to a carcinoma of the papilla of Vater." Courvoisier was a surgeon and, therefore, a very able and precise investigator. He himself accepted that in 18 per cent of the cases this rule did not work. In every 1,000 cases of jaundice with a palpable gallbladder he was wrong 180 times. The conclusion of Courvoisier was so correct that even today in a patient with deep jaundice and a palpable gallbladder, at operation usually a carcinoma of the head of the pancreas, or a carcinoma of the ampulla of Vater is found.

For palpation of the abdomen the patient should be completely relaxed and lie flat in bed. Some patients need a small head pillow, others a larger one. Some patients relax their muscles better when they flex their knees. Then, just as important, the palpator should be relaxed and should sit down. He should not stand, as a busy consultant customarily does, and absent mindedly poke in the abdomen, in the meantime talking to his audience. During such a performance correct palpation is impossible. In my experience many gallbladders are very well palpable, but are not palpated. The increasing amount of exceptions to the rule of Courvoisier is due, in my opinion, to bad palpation.

Dr. DeFeo correctly said that in the presence of a hepatoma as a rule damaged liver function is found. Hepatoma is a hepatocellular tumor, a proliferation of liver cells which often can hardly be differentiated from normal liver cells. The histological structure of many hepatocellular hepatomas is very much like the normal liver. Often the liver biopsy is declared normal and a hepatoma is present nevertheless. In one patient where the liver biopsy was said to contain only normal liver tissue, later in the puncture channel a metastasis developed. This proved that in the material removed by liver puncture, carcinoma cells must have been present. All this notwithstanding, the liver puncture may be of great importance for the diagnosis of hepatoma. This is for instance true in a patient whose liver in the course of a year or shorter, has rapidly increased in size to a hard, nodular mass. Then on clinical grounds the diagnosis of a neoplasm of the liver is certain. If now a liver puncture is performed and a cirrhosis is found, the diagnosis of a hepatoma is in order. Firstly, hepatoma, in far the greater part of the cases, is secondary to cirrhosis. Secondly, the patient cannot have a cirrhosis only, because within six months the liver has rapidly grown in size and the general condition has deteriorated. He must have a neoplasm of the liver because the liver has rapidly grown in size and changed its consistency. It is remarkable how rarely tumors metastasize in a cirrhotic liver. Therefore, if a liver is cirrhotic, as proved by biopsy, and is malignant, as proved by clinical observation, then there is hardly ever a metastatic carcinoma but nearly always a hepatoma present.

Liver function tests are of great clinical importance, but this statement must be qualified. A positive cephalin-cholesterol flocculation test indicates degeneration of the liver cells, and is of great importance. The same holds true, perhaps for the thymol turbidity test. A negative cephalin flocculation test, however, has no differential diagnostic importance because this can also occur in hepatitis.

The reverse is true of the alkaline phosphatase of the serum. There are many reasons why the alkaline phosphatase can be increased. The increase may be due to obstructive jaundice, but also to liver disease in which proliferation of the cholangioles is present, and in diseases of the skeleton in which osteoblastic activity is increased. Therefore, an increased alkaline phosphatase may be due to many different factors. But if the alkaline phosphatase is negative,

then an obstructive jaundice is highly improbable. Thus, the results of the most popular forms of liver function tests, cephalin flocculation and alkaline phosphatase, must be defined in the following way. A positive flocculation is conclusive for the diagnosis of damage to the liver parenchyma; a negative reaction does not exclude such damage. Normal alkaline phosphatase is important because it practically excludes obstructive jaundice. But an increased alkaline phosphatase may or may not result from obstruction. It may also be due to a change of the liver parenchyma or to proliferation of cholangioles.

We do not know whether luetic hepatitis actually did exist, even if hepatitis was frequently encountered in the secondary stage of syphilis. Now, in retrospect, most of these cases may well have been due to homologous serum jaundice, because all these patients were treated with injections, – mercury, bismuth, arsphenamine.

When I was a student an exploratory puncture had become an old fashioned method and had been replaced by open biopsies. I remember I was called, as a student, before the class to examine a patient with a cervical cyst. The chief asked, "What is this?"

"A cyst, sir."

"What kind of a cyst?"

"I don't know, sir."

"How would you decide the nature of this cyst?"

"I would puncture it, sir."

The chief said, "Go and sit down. I am ashamed that you are my pupil. This cyst should be removed and examined microscopically."

Nowadays punctures again are popular including those of the liver. A biopsy by puncture which would have been ridiculously old fashioned about 40 years ago is again a modern method! If 40 years ago jaundice lasted longer than three weeks, an exploratory laparotomy was performed. Nowadays we rely upon indirect liver function tests and upon liver biopsy for this decision. In punctures of a parenchymatous organ an occasional accident must be expected. Occasionally patients have to be operated as an emergency because hemorrhage has developed after the puncture. The Vim-Silverman needle is not a very good instrument, even if it is used all over the country. The modification devised by Franklin, and the–expensive–needle of Terry, both used in Cook County Hospital, are much better instruments, causing fewer risks and providing better specimens.

In hepatitis, with a high cephalin flocculation, a high thymol turbidity, normal cholesterol, increased prothrombin time and a normal alkaline phos-

phatase, a liver biopsy is hardly needed. But in the so-called cholangiolitic hepatitis, where the cephalin flocculation is normal, and the alkaline phosphatase is increased, the liver function tests are inconclusive. Unfortunately, in this form of hepatitis the histologic lesions found in the liver biopsy are often scanty and may be similar to changes observed in obstructive jaundice.

Therefore, in cholangiolitic hepatitis where we really could use the liver biopsy for the diagnosis, the pathologists have great difficulty to recognize the characteristic changes in the infinitesimal sliver of liver substance which represents the result of a liver biopsy.

Dr. Owen H. Wangensteen:—I do not know why I should inject myself into this discussion. Every abdominal surgeon, however, is concerned with the problem of jaundice. What we like to know essentially, if we can have the information from our internist colleagues, is whether or not a given case of jaundice is a surgical problem.

I was delighted to hear Dr. Snapper's allusion to L. G. Courvoisier of Basle, Switzerland, who wrote the first surgical monograph on surgery of the biliary tract. It was the surgeon, Courvoisier, who first pointed out the significance of a palpable gallbladder in the differential diagnosis of obstructive jaundice.

Now, we are not too much concerned whether the internist makes a correct diagnosis, but we are concerned over not operating upon nonsurgical kinds of jaundice. I would infer even from this discussion that we need more light on the subject than we have today, because we hear of cholangiolitic jaundice accompanying the administration of drugs like chlorpromazine. And there are still occasions when an exploration must be done to clarify the nature of the jaundice.

When I was a medical student, I had what was called catarrhal jaundice. I think I was hospitalized for two days. During the last few years I have had two surgical residents who were diagnosed as having a form of hepatitis of transient duration. I suspect that these are very much the same as what was called catarrhal jaundice 35 years ago. The first resident, shortly after World War II was hospitalized for three months, and kept in bed. My last resident with hepatitis was hospitalized for six weeks, and given a nice vacation for an additional period of time. Whether such vacations or that amount of bed rest are necessary or helpful in the repair of the liver cells, is probably still a good question. More information has made internists more conservative in their outlook upon this problem.

I must confess I am completely at sea about wherein the differential diagnosis lies between the so-called catarrhal jaundice and other kinds of homologous serum jaundice that internists speak of so glibly.

What I want to know is being confronted with a patient who has jaundice—if the information is available—is whether the patient has surgical jaundice. When it comes to surgical jaundice, I think that after adequate preoperative preparation, the thing to do is to have a look. The old Chinese proverb is still good. All the dialectics which you will hear from this platform are not nearly as good in the differential diagnosis of some kinds of jaundice as is a good look of a knowing eye, and the feel of an experienced hand upon exploration of the ducts.

Every now and then, however, one is led into exploring a patient, in which situation one feels obliged to say upon conclusion of the operation: "I certainly have not helped the patient very much."

Cancer of the head of the pancreas is an operable condition. Many surgeons would have us believe that the mortality is so large that one should no longer do the radical operation. This operation has been successfully done over a period of years in my Clinic by a number of surgeons. In fact, it would seem that the younger and more intrepid and courageous surgeons are doing a better job with this problem than the older and more conservative group. Dr. Bernard Zimmermann currently is doing these operations in my clinic. He has shown me two patients past 80 years upon whom he has successfully done the Whipple operation for excision of the head of the pancreas. There are, to be certain, a lot of complicated physiologic and surgical problems involved in this situation. If the operation is carefully done, and the pancreatic duct can be replaced in the jejunum, I think the patient is improved greatly thereby.

I am certain that as surgeons gain more experience with this operation and do it well, the number of five-year cures reported following excision of the head of the pancreas for cancer will increase materially.

There is one condition having to do with stones in the gallbladder that I think should be given more careful notice by all of us. I allude to the presence of a fibrosis and narrowing of the biliary ampulla—a condition which may represent an atretic termination of the bile duct. It is strange how often one encounters the presence of stones in the gallbladder when such an atretic ampulla is present. In fact, one must ask himself: are the gallstones found in consequence of the ampullary obstruction? The presence of gallstones and a dilated, thin common bile duct constitutes indication for a duodenotomy and a look at the ampulla. One should not merely remove the gallbladder. One should explore the termination of the ampulla under these conditions. In fact, I have begun to ask myself and my colleagues if gallstones may not be the result of obstruction at the biliary ampulla. In fact, we have begun in good risk patients, even in the presence of extensive operations for cancer, if gallstones are found in the gallbladder, to have a look at the ampulla. It is strange how often an atretic termination of the bile duct seems to be a common denominator of gallstones.

In exploring the bile ducts, the surgeon automatically, if he is right-handed, goes to the left side of the patient after mobilization of the duodenum. One of the smaller Bakes' dilators is introduced into the open distal end of the cystic duct; upon the slightest suggestion of difficulty in advancing the probe, the surgeon with the tip of the probe pointed up toward him and using no force whatever, makes a transverse incision in the anterior duodenal wall between two well placed very fine guy sutures; the tip of the probe can then be felt through the posterior duodenal wall; one looks for the bile duct opening; the probe should never be pushed, if it does not advance readily, lest one make a false passage in the anterior wall of the bile duct into the duodenal lumen. It is striking how often in the presence of gallstones, one finds fibrosis or narrowing of the termination of the bile duct. A dilated common bile duct without stones usually is present. I terminate the operative procedure by slitting the stenosed ampulla.

In earlier years, we used to hear a lot about regurgitation cholangitis. If one has performed sphincterotomy, it is astounding when patients are given barium meals, to note how often the barium regurgitates into the bile duct from the duodenum. Symptoms following such regurgitations in my experience have been very few.

If a patient should get cholangitis following this procedure, my suggestion would be to do a Billroth II operation, isolating the duodenum by inverting it as a blind loop, thus minimizing the opportunity for food to find its way into the common bile duct.

Sphincterotomy for an atretic ampulla is a very helpful procedure. The sphincter of Oddi, it should be said, parenthetically is a source of protection for all of us. Dr. Allen Boyden, formerly of our institution and now at the University of Washington in Seattle, has done a lot to clarify the anatomy of the sphincter of Oddi. Many surgeons, in operating for the relief of iatrogenic strictures of the common bile duct, have come to prefer direct choledochoduodenostomy to reconstruction of the duct. Dr. W. J. Mayo long years ago alluded to the circumstance that such direct anastomoses of bile duct to duodenum, circumventing the sphincter of Oddi, gave excellent results. More recently, Dr. Waltman Walters of Rochester, Minn. finds their best results in strictures of the common bile duct are with the direct anastomosis. Similarly, Dr. Richard Varco, of our institution, finds that the best results were in patients in whom the anastomosis had been made directly between the proximal end of the bile duct and the duodenum. Perhaps the sphincter of Oddi is not as necessary as many of us have been led to believe.

Finally, as a surgeon, I would say what information we want from our internist colleagues is: "Is this a case of surgical jaundice or not?" For the resolution of the nature of a given case of surgical jaundice, I think even

experienced surgeons are helped by having access to the virtues of all the differential preoperative tests known. Yet, exploration must be relied upon now and then to establish the diagnosis.

Hepatomas of the liver are curable lesions. I have removed 3 such lesions. Excision of extensive segments of liver tissue is not the problem that it was once thought to be. The liver is a fibrous structure. I think it is easier to take a slice out of the liver than to repair a needle puncture of the spleen. Unless the spleen is fibrous in texture, a needle puncture or tear provokes the surgeon to remove the spleen. Not so with the liver, the control of hemorrhage from the liver in the excision of small segments is not a formidable problem.

The problems in dealing with surgical excision of liver tissue are three: first, in working at the root of the hepatic veins: air embolism. If a small hole is cut in an hepatic vein and the patient takes two or three breaths, it is usually too late to do very much about it. The right heart gets full of air. The surgeon must recognize therefore that, the fibrous bands about the points of entry of the hepatic veins into the vena cava make the hazzards of air embolism real unless the veins are clamped before they are opened. The problem of air embolism is not a serious one if one handles the situation intelligently.

The problem of control of bleeding in the removal of large segments of liver tissue is still one of the major problems. One may occlude the entire hepatic afferent inflow to the liver, but only for short periods of time. We know that refrigeration lengthens the interval over which occlusion of the hepatic inflow is tolerated. Momentary occlusion of the hepatic artery is not signifiicant.

Cancer in the liver does not mean the situation is inoperable. I confess, however, as far as I know, I have not cured a single patient with metastasis into the liver. When I contemplate wide excision of liver tissue, I usually employ the extrapleural sternal splitting incision; the pericardium is opened up and a tape is placed about the intrapericardial portion of the vena cava. I have employed this maneuver too in the excision of a thrombus from the vena cava, in the presence of a large hypernephroma of the kidney. The vena cava then, if need be, can be pulled up taut. It is odd how occluding the vena cava at that level will push the blood pressure down to very low levels (0 to 40 mm Hg.). That much is the body dependent upon the return of blood from the abdomen and the lower extremities if the aorta is not occluded.

We have cured several patients with hepatic extensions, whether from a hepatic carcinoma of the gallbladder, the right colon or from the stomach, for periods of time as long as ten years or more. The liver, I believe, will grow faster than cancer. Surgeons need to master the technics of excising large segments of liver without inviting complications, which are difficult to cope with.

The third important problem pertinent to this whole discussion of operating upon the biliary passages and liver is the prevention of bile leaks. It is one of the important causes of mortality. When a T-tube is placed in the common bile duct, it is necessary to be certain that the opening in the common bile duct is completely closed; it may look tight, but after placement of sutures, the duct tube should be irrigated to look for leaks. Bile draining (outside an inlying biliary duct tube) through a Penrose drain means that the surgeon's management of the problem of potential bile leak was not adequate. Bile is a very viscid fluid. I have seen a patient die, draining bile to the exterior freely; yet at autopsy, more than a liter of bile was in the belly. Every patient with an inlying peritoneal drain should be placed flat on his belly for many hours each day in the early convalescence. Water can only run downhill. If a patient a few days after operation upon his biliary tract has leucocytosis, and some fever, and bile is draining out through a Penrose drain lying beside an intraductal tube, I find myself saying to the Surgical Resident: "Do a suction-tip drainage to remove that collection of bile. There must be a collection some place or that patient would not continue to drain bile outside the T-tube."

This expedient of suction-tip drainage, performed through a lateral stab wound of the abdominal wall, has saved many lives in our Clinic. A tonsil type of sucker is used with a long handle with provision for interrupting which is described and pictured in my book on intestinal obstruction (1955).

One other thing: in removing the gallbladder, the surgeon now and then divides a tiny anomalous bile duct without observing its occurrence. If one will only place routinely a small Robinson catheter (No. 8 or 10 French) into the cystic duct when he removes the gallbladder, the bile will flow more readily through that catheter than through a tiny divided ductule you cannot see. This is a simple, but a very useful, expedient.

With reference to needle liver biopsy, I would only say it is something I have not done. The internists do it in our Clinic. Our surgeons have been called upon occasionally, I know, to drain a subdiaphragmatic abscess in a few cases following such liver biopsies; they have been requested to drain the peritoneal cavity because the gallbladder has been punctured and bile has leaked out. In one instance the hepatic artery was punctured and continued to bleed. Fortunately, the surgeon was able to stitch up the hole in the hepatic artery. I would wonder, with the needle placed as Dr. Beman showed us, whether he would not puncture the pleural cavity once in a while. I suppose it really would not make too much difference. I think Ronald Ross of the Indian Medical Service, long years ago, was knighted by the British Government for pointing out that amebic abscess should be aspirated by needle and not incised and drained, because one then introduces pyogenic infection.

I feel even more strongly about peritoneoscopy. Just because a patient has cancer and has a few implants does not mean that the lesion is inoperable.

It is amazing now and then what a surgeon can do if fortified with an aggressive attitude in operating for cancer. A little cancer on the parietal peritoneum or on the liver, by no means, constitutes a contraindication to operation. Even palliative operations prolong life. None of us expects to reach the other shore; but as long as life is pleasant and the company is congenial, most of us like to keep our frail crafts afloat. That is an experience which I have been learning in talking to patients in the Out-Patient Clinic. No matter whether a man is 80 or 50, his answer is almost invariably the same: "If you can do something to make me feel better for a period of time, I am in your hands, and I will do whatever you say." Patients are as malleable as clay, if one will only deal with them frankly, openly and honestly.

BIOPSY OF THE LIVER*

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The diagnosis of primary disease of the liver, or of systemic disease in which the liver is involved, can be made in many instances by clinical and laboratory studies without liver biopsy. There are frequent situations, however, where only an examination of liver tissue itself is the deciding factor in the establishment of an absolute diagnosis. Laparotomy can only be sparingly used for this purpose because of the frequent refusal of the patient to grant permission and because of the occasional hesitancy of the surgeon to operate upon patients with a serious affection of the liver. The work of Iverson and Roholm[1] in 1939, although it appeared almost 50 years after the first needle biopsies were successfully performed, was the real stimulus which started the widespread use of this procedure. Since then hundreds of manuscripts have been written and many thousands of cases have been reported in the medical literature proving its value in diagnosis, prognosis and evaluation of therapeutic regimens. Intensive studies have been made to correlate the numerous liver function tests with histologic changes noted in the biopsy. It is the purpose of this paper to discuss certain aspects of the results obtained in 166 liver biopsies performed on 151 patients at the Beth-El Hospital.

Technic and Material

Biopsy during laparotomy was performed in 36 cases. Most of these were done prior to the time that needle biopsy was in common use. Eight biopsies were performed because, during an abdominal operation for some other condition the liver appeared to be grossly abnormal. Two patients with hepatomegaly, in whom the biopsy, performed during laparotomy, showed portal cirrhosis, died within 72 hours after surgery. The probable cause of death was pulmonary embolism. One patient died 10 days postoperatively as a result of peritonitis. In contrast to liver puncture adequate liver tissue was removed in all cases of biopsy during laparotomy to establish a definite diagnosis.

The Vim-Silverman needle was used to perform 130 biopsies in 115 patients. The subcostal approach was used only when the liver was massively enlarged, or where it was desired to obtain tissue from the left lobe of the liver. In all of the remainder the intercostal approach was used. Preoperative sedation was

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obtained with demerol. Patients with prolonged prothrombin time or any other bleeding tendency were not biopsied unless these abnormalities could be corrected. Also excluded were patients with severe congestive heart failure or intense obstructive jaundice. The skin and subcutaneous tissues down to the Glisson's capsule were infiltrated with 2 per cent procaine hydrochloride solution. The needle was inserted in the right eighth or ninth intercostal space in the midaxillary line. In one instance with a transposition of the viscera the approach to the liver was through the left ninth intercostal space. The patient was instructed to hold his breath after a deep expiration at which time the needle was inserted into the liver, the biopsy quickly performed and the needle withdrawn. The patients were kept at rest for 12 hours following biopsy. The

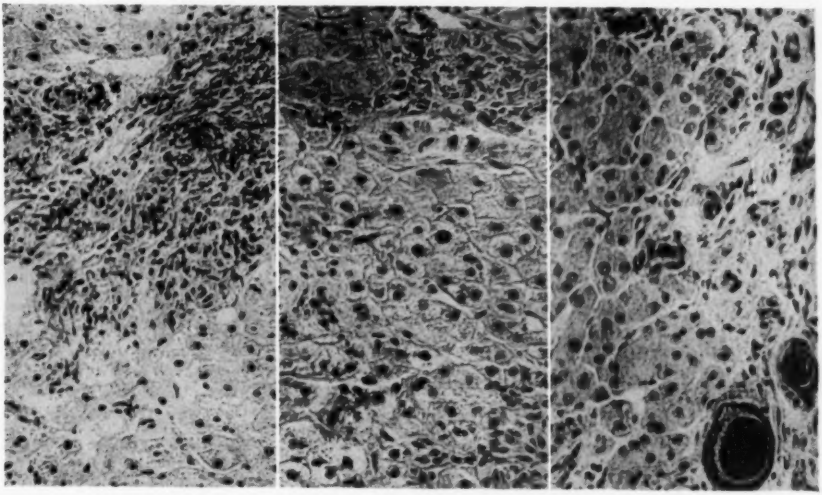

Fig. 1a Fig. 1b Fig. 1c

Fig. 1a—Viral hepatitis—cholangiolitic type.
Fig. 1b—Viral hepatitis—parenchymal type.
Fig. 1c—Extrahepatic obstruction.

only rather frequent complaint after a needle biopsy consisted of pain either at the site of the insertion of the needle or in the right shoulder during deep inspiration. This was easily controlled with demerol. Among our patients there were no complications such as bleeding, infection or bile peritonitis. There were no fatalities. In this connection it should be mentioned that Neefe[2] speaking before this body in 1952 reported 2 deaths in a group of approximately 3,500 biopsies and 5 cases of serious hemorrhage in a series of 2,235 cases.

In one of our patients the needle was misdirected and normal renal tissue obtained. In another patient purulent material was aspirated which on smear and culture was found to contain acid-fast bacilli. Further study of this patient

disclosed a tuberculous right kidney. In six cases the pathologist reported that inadequate tissue had been removed to permit a definite diagnosis.

Schiff[3], in his report of the clinical value of needle biopsies performed in over 700 patients without a fatality, lists 9 categories where the usefulness of the procedure has proven its worth. We have found his classification a good one and shall use it with certain revisions for the presentation of our cases. The following case summaries and microscopic specimens have been selected to exemplify the different categories.

1. Exclusion of hepatic disease in the presence of suspected liver enlargement or abnormal liver function tests.

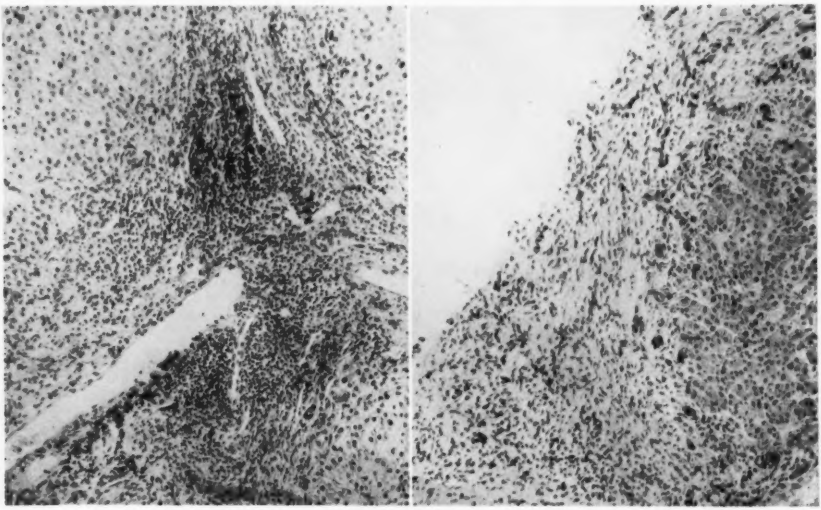

Fig. 2a Fig. 2b

Fig. 2a—Early changes with cholangiolitic inflammation (1949).
Fig. 2b—Advanced changes with definite cirrhosis (1953).

In seven patients of this group the liver was palpable from 2 to 4 cm. below the right costal margin. All these patients had gastrointestinal symptoms. There were histories of preceding illnesses which might have resulted in liver damage such as hepatitis, diabetes, excess ingestion of alcohol and primary malignancy of the gastrointestinal tract or some other system which had previously been operated upon. The liver biopsies showed normal liver tissue. In view of this result it was possible to rule out the presence of liver disease. Further clinical observation or subsequent surgery confirmed the biopsy impression. It follows that the presence of a palpable liver does not necessarily justify the diagnosis of liver disease.

Four such patients showed significantly altered liver function tests. Low total serum protein values with inverted albumin/globulin ratios, positive cephalin flocculation and thymol turbidity tests were present in a patient in whom the biopsy was negative. This patient was subsequently found to suffer from a subacute bacterial endocarditis. Three other patients had slightly enlarged livers and positive cephalin flocculation tests during the course of undiagnosed febrile illnesses. The liver biopsies were normal. These patients subsequently made complete recoveries and no evidence of liver impairment remained.

Needless to say, changes in the serum globulin may be due to many causes other than liver disease.

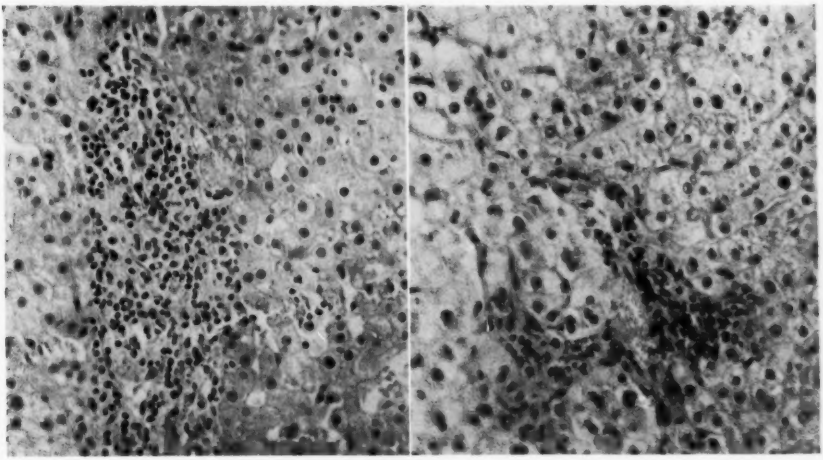

Fig. 3a Fig. 3b

Fig. 3a—Hodgkins' disease.
Fig. 3b—Leukemic infiltration.

Differentiation of Medical and Surgical Jaundice

Steigmann et al[4] point out that, despite the best possible combination of available liver function tests, even the experienced clinician finds that in 4 to 5 per cent of patients with jaundice the differential diagnosis cannot be established with certainty.

Four patients with jaundice presented symptoms and a clinical course consistent with the diagnosis of viral hepatitis. The only abnormal liver function test, however, aside from elevated serum bilirubin values, was a moderate elevation of the alkaline phosphatase. The latter result was evidently due to intrahepatic obstructive jaundice because in these cases the liver biopsies re-

vealed the presence of bile thrombi in the smallest biliary radicles. In no instance was dilatation of the larger bile ducts found in the histologic sections. The pathologic diagnosis was the cholangiolitic variety of viral hepatitis. One of these patients also complained of recurrent right upper quadrant pain. An attempt to visualize the gallbladder and bile ducts was unsuccessful. Because some examiners felt that notwithstanding the absence of dilatation of the larger bile ducts a common duct calculus obstruction had not been ruled out, exploratory operation was performed. The gallbladder and extrahepatic ducts were free of calculi or other pathology. All of these patients made uneventful recoveries.

A 76-year old female was admitted because of increasing, painless jaundice, clay-colored stool, itching and bilirubinuria. The admission diagnosis was ob-

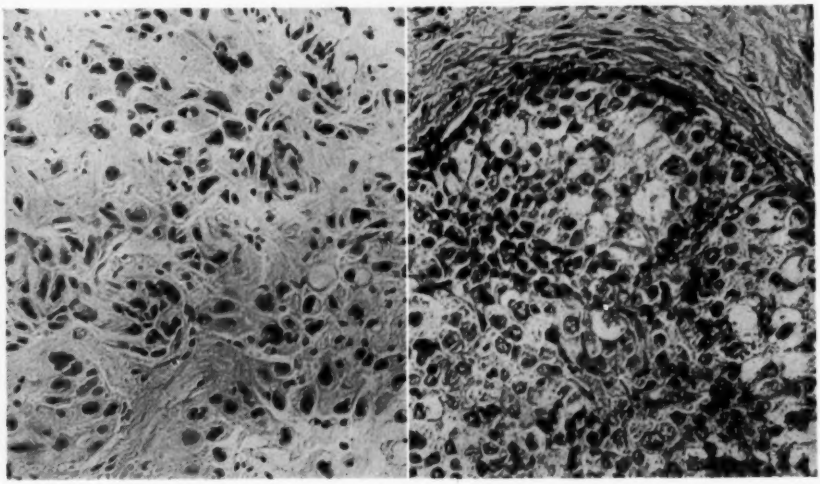

Fig. 4a Fig. 4b

Fig. 4a—Metastatic adenocarcinoma.
Fig. 4b—Primary liver cell carcinoma.

structive jaundice, probably due to carcinoma of the head of the pancreas. The laboratory tests showed an increased serum bilirubin, a 4 plus cephalin flocculation and 12 units of thymol turbidity. The cholesterol ester content had decreased to less than 40 per cent of the total cholesterol. The abnormal liver function tests cast doubt upon the diagnosis of obstructive jaundice. Liver biopsy showed the typical histologic appearance of viral hepatitis. She made an uneventful recovery after conservative medical treatment.

Two patients were admitted with painless jaundice and a clinical course consistent with viral hepatitis. This diagnosis seemed doubtful when the liver function tests were proved to be normal, aside from an elevated serum bili-

rubin and moderately elevated alkaline phosphatase. The stools were not acholic. Liver biopsy showed evidence of cholangitis with bile stasis in the larger bile ducts. In view of the latter finding extrahepatic obstruction was diagnosed and at operation partial obstruction of the common duct by calculus was found in both cases.

Comment:—Liver biopsy is of definite value in helping to differentiate between medical and surgical jaundice (Figs. 1a, b and c). In the borderline cases, where the history is not typical and the liver function tests negative or equivocal, liver biopsy may be the only means by which one can decide for or against surgery. When, however, the result of the biopsy is not diagnostic, laparotomy may have to be resorted to in order to be certain that one is not dealing with extrahepatic ductal obstruction.

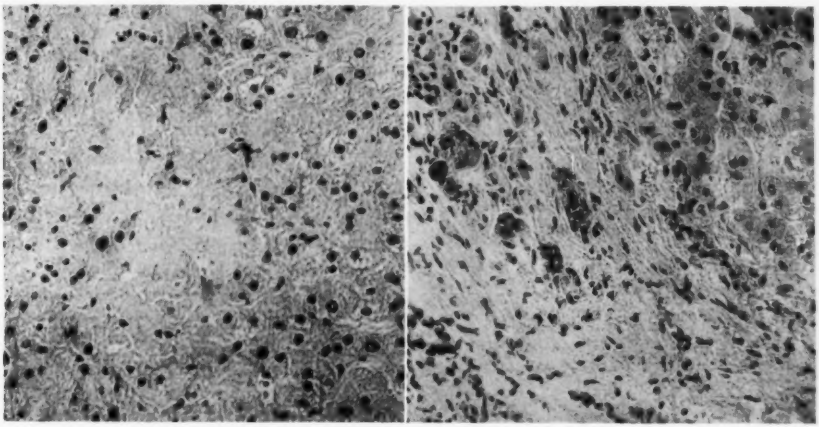

Fig. 5a Fig. 5b

Fig. 5a—Amyloid.
Fig. 5b—Hemochromatosis.

Observation of the Natural Course of Liver Disease

Serial biopsies are of great value in studying the changes which take place in the evolution of chronic disease or the resolution of acute disease of the liver. Deschamps and Steer[5] showed that, in patients with hepatitis of unusual severity, liver biopsy sometimes revealed rather extensive changes even after the results of physical examination and laboratory study seemed to indicate a complete recovery. Volwiler, Jones and Mallory[6] in studying the results of treatment of fatty cirrhosis, stated that after the most careful clinical scrutiny of the patient the histologic phase of the liver disease present cannot be accurately predicted. In their studies the microscopic examination of liver tissue was frequently the only means of determining the changes which developed during

clinical observation. The focal necrosis and cellular infiltration diagnostic of active hepatitis may completely disappear, or they may progress to fibrosis, bile duct proliferation or fatty changes. The latter processes may be reversed or may ultimately lead to the development of hepatic cirrhosis. Only repeated biopsies can trace these progressive or regressive changes. The following is an illustrative case.

Case 200783:—R. G., a 47-year old white, married female was admitted to Beth-El Hospital in September 1949 because of jaundice, weakness, anorexia and weight loss. The urine showed the presence of bilirubin and increased urobilinogen. The icterus index was 40.5, the alkaline phosphatase 2.4 Bodansky units, the zinc turbidity 12 units, the cephalin flocculation 3 plus and the total cholesterol 720 mg. per cent. Liver biopsy showed moderate fatty infiltration, dilatation of the biliary canaliculi in which many bile thrombi were present and some local round cell infiltration in the portal zones. In the absence of dilatation of the larger bile ducts this result was interpreted as being indicative of intrahepatic small bile duct obstruction. Because of the high cholesterol content xanthomatous biliary cirrhosis was considered a diagnostic possibility but this diagnosis was later discarded. The patient improved appreciably under treatment but the jaundice never subsided. In November 1950 the jaundice and liver function tests were essentially the same. Repeat biopsy now showed a histologic picture consistent with a diagnosis of cholangiolitic biliary cirrhosis. In June 1952 she was readmitted to the hospital because of pyelonephritis which rapidly cleared with antibiotic therapy. Severe back pain which she experienced prior to and after this infection was found by x-rays to be due to compression fractures of the sixth dorsal to and including the second lumbar vertebrae. The serum calcium was 9.2 mg. per cent, the phosphorus 1.8 mg. per cent, and the alkaline phosphatase 10.8 Bodansky units. Liver biopsy was similar to that taken on the previous admission although it showed a somewhat more advanced degree of biliary cirrhosis. In February 1953 she was readmitted because of persistent vomiting, mental torpor, nasal hemorrhage and generalized ecchymoses. She was intensely jaundiced. There were small, scattered cutaneous xanthomata. The liver was smaller than before but the spleen was markedly enlarged. The prothrombin time was less than 1 per cent of normal. Blood chemical studies were essentially unchanged. Additional compression fractures of the upper thoracic vertebrae were noted which were now felt to be due to osteomalacia resulting from prolonged biliary steatorrhea[7]. Biopsy showed severe biliary cirrhosis. The patient's course was steadily downhill with increasing evidence of liver failure. She died 4 months after admission. Study of the liver after death showed extensive biliary cirrhosis.

Comment:—This patient, who initially showed the clinical, laboratory and biopsy findings of cholangiolitic hepatitis progressively developed the picture of cholangiolitic biliary cirrhosis. The serial biopsy studies taken at approximately annual intervals over a period of 4 years clearly depicted the histo-

pathology which reflected itself in the clinical findings and liver function tests (Figs. 2a and 2b).

Correlation of Liver Function Tests with Pathologic Changes in Liver Tissue

Numerous students of this subject have attempted to associate abnormalities of liver function tests with morphologic changes in the liver. Lichtman[8] stated at one of our meetings that there is only a superficial agreement between the results of the tests and structural changes as judged by routine histopathologic technics. The failure to find any such correlation should cast no doubt upon the value of either the liver function tests or the biopsy. In diseases where multiple areas of focal damage are distributed throughout the liver, the needle may well strike a normal zone. In such cases the biopsy will appear normal in the face of abnormal laboratory tests. It is known too that liver functions may proceed in a normal fashion as long as only a small amount of normal hepatic tissue remains. The tremendous power of the liver to regenerate after disease or injury must be a source of error. If one were to fortuitously insert the needle in such a regenerating liver area, the histologic appearance of the cells might be normal though in the surrounding area severe cytologic changes would be present. Berk and Shay[9] aptly state that the liver function test and biopsy each supplies information peculiar to itself. These procedures must be considered complementary and incapable of being substituted one for the other. Popper et al[10] feel that where the structural changes are diffuse, even if inconspicuous, liver function is severely impaired. Norcross et al[11] state that, aside from neoplastic involvement and focal necrosis, most pathologic processes involving the liver are diffuse and that the pathology throughout the liver usually is accurately represented by a single specimen. This has also been our experience. In such diffuse diseases as viral hepatitis there was a high degree of correlation. In other diseases, focal in character, such as metastatic carcinoma there was hardly any correlation whatsoever. It should be stressed that in diseases affecting such an organ as the liver, the history, physical examination and acumen of the clinician are the all important factors in arriving at a definite diagnosis which then however should be confirmed—or refuted—by subsequent laboratory studies.

Diagnosis of Granulomatous and Fungus Diseases

In two cases of Boeck's sarcoidosis the liver biopsies failed to show the granulomatous lesions. This is in contrast to the results of other authors who report a high percentage of positive needle biopsies in this disease. In one case of unexplained fever with hepatosplenomegaly a bone marrow culture proved the presence of histoplasmosis. Although postmortem examination confirmed the diagnosis of histoplasmosis, liver biopsies during life were unrevealing. Gross examination of the liver in such cases would undoubtedly show numerous areas of involvement. The conclusion must therefore be drawn that the small

amount of tissue removed was from an uninvolved area. This should not militate against the diagnosis when the clinical course and other studies are positive. Perhaps repeat biopsies in another region of the liver would reveal the pathology.

Diagnosis of Lymphomatous Diseases

Hepatomegaly, with or without splenomegaly, may sometimes be the only abnormal physical finding in patients suffering from this group of disease. Even in patients with significant adenopathy, biopsy of a lymph node may be reported as showing only chronic lymphadenitis. The bone marrow examination may also be normal. Such patients may proceed for a long time with fever of undetermined origin. Our experience with liver biopsy in such cases has been gratifying. Three patients showed the typical histologic picture of Hodgkin's disease (Fig 3a). One patient, whose initial biopsy was reported as an undifferentiated malignant tumor, showed on a subsequent biopsy the typical picture of lymphosarcoma. X-ray therapy proved very beneficial in ameliorating the patient's complaints and returning the temperature to a normal level. In two cases the suspected diagnosis of agnogenic myeloid metaplasia was confirmed by finding extramedullary hematopoiesis in the liver biopsy. In a case which only subsequently could be proved to be myeloid leukemia, an early biopsy showed leukemic infiltration of the liver (Fig. 3b).

Verification or Detection of Neoplasia of the Liver

In numerous patients with hepatomegaly in whom primary carcinoma was known to be present in the gastrointestinal tract or in some other organ, liver biopsy was performed. Not all such livers were nodular or massively enlarged. Although, as mentioned above liver punctures in metastatic liver disease may well be negative, there were also many cases where the finding of malignant tissue obviated the need for operative procedures. In a few of these patients operations were performed for palliative reasons. In two instances in which densities were present in the lung, bronchoscopy, cytologic studies of the sputa and bronchial washings were negative. Biopsies of slightly enlarged livers in both of these cases disclosed metastatic carcinoma (Figs. 4a and b). This made exploratory thoracotomy unnecessary. Melanocarcinoma was detected in one patient with hepatomegaly who had an eye removed a number of years before. In two cases where carcinoma was unsuspected, liver biopsy disclosed metastatic carcinoma. This led to the use of further procedures which aided in localizing the primary focus. The following is the report of one such case.

Case 188324:—A. K., a 68-year old male, was admitted to the hospital because of recent weight loss. He stated that on occasion food seemed to get stuck in the region of the lower end of the esophagus. After admission, however, he was able to ingest a regular hospital diet without difficulty. In fact, his appetite improved and he gained weight. Complete gastrointestinal survey,

with particular attention to the esophagus, proved negative. He was almost ready for discharge when he complained of some pain in the right upper quadrant of the abdomen and the liver edge became palpable just below the right costal margin. He also developed a low grade fever. Liver biopsy was reported as showing normal liver cells. Because the temperature persisted and slight icterus was noted a repeat liver biopsy was performed which now revealed metastatic carcinoma with several foci giving the appearance of epidermoid cancer. A repeat esophagram and gastrointestinal x-ray series were again negative. Esophagoscopy was then performed which disclosed a flat, infiltrating lesion in the lower end of the esophagus. Biopsy of this lesion disclosed epidermoid carcinoma. The patient subsequently died and at postmortem examination the diagnosis of primary carcinoma of the esophagus with diffuse metastases to the regional lymph nodes and liver was confirmed.

Diagnosis of Metabolic Disturbances

Liver biopsy may be the only means during life of establishing a definite diagnosis of amyloidosis. Recently renal biopsy has also been utilized for this purpose. In a number of cases where this disease was tentatively diagnosed, both renal and liver biopsy revealed other reasons for the clinical manifestations. On the other hand amyloid was found on the liver biopsy of one patient where the presence of amyloid had not been suspected (Fig. 5a).

We have had 3 established cases of hemochromatosis, two of which were confirmed by liver biopsy[12]. One patient had been treated for many years for portal cirrhosis presumably due to alcohol intoxication. The liver biopsy showed definite evidence of pigment cirrhosis and the skin biopsy showed focal iron accumulations (Fig. 5b). A summary of the following case indicates the extreme value of liver biopsy in the third patient.

Case 193027:—L. G., a 38-year old male butcher, was admitted to Beth-El Hospital, Feb. 3, 1949 because of vague complaints of abdominal and chest pain. Physical examination showed no pigmentation of skin or mucous membranes, and sparse axillary and pubic hair. The liver and spleen were felt 2 cm. below the costal margins. The urine and blood count were normal. The fasting blood sugar was 86 mg. per cent. The cephalin flocculation was 3 plus in 24 hours and the prothrombin time 47 per cent of normal. Bromsulfalein excretion, zinc turbidity, total proteins, albumin/globulin ratio, alkaline phosphatase, cholesterol, cholesterol ester and hippuric acid excretion were all normal. The glucose tolerance test showed a tendency toward a diabetic curve (94.3 mg. per cent, 125.8 mg. per cent, 222 mg. per cent, 117.6 mg. per cent, 83.3 mg. per cent). X-ray studies of the gastrointestinal tract, gallbladder, spine and long bones were negative. Liver biopsy showed definite evidence of portal cirrhosis with extensive hemosiderosis. The skin biopsy was negative. This patient has been treated by repeated vene-section with removal of 500 c.c. of blood at

monthly intervals and has remained in fair health since that time. Repeat biopsy has shown no further progress of the disease.

Evaluation of Therapy in Liver Disease

We have not utilized liver biopsy for this purpose. It is, however, understandable that by the use of this method, in conjunction with liver function studies and the clinical course of the patient, a satisfactory form of treatment of different liver diseases can ultimately be outlined. There is much difference of opinion regarding the value of particular diets, lipotropic agents, the corticosteroids, physical rest, etc. Schiff[3] and Volwiler et al[6] in their excellent biopsy studies show the effect of therapy in fatty cirrhosis. It is difficult to accept the recent recommendations for early activity following clinical and laboratory improvement in cases of viral hepatitis. Popper et al[10] emphasize the importance of bed rest in this condition by showing the marked deterioration of the histologic picture of the liver even in the recovery stage if a biopsy is repeated after exercise.

Summary

1. An analysis of 166 biopsies of the liver has been presented. Thirty-six were performed during laparotomy: 130 were performed with the Vim-Silverman needle in 115 patients.

2. Needle biopsy, in contrast to laparotomy biopsy, has not been attended by either morbidity or mortality.

3. The value of liver biopsy in diagnosis, prognosis and evaluation of therapy has been stressed.

4. The lack of correlation of liver function tests with histopathologic changes in the liver has been noted. The importance of both procedures has been emphasized.

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Discussion

Question:—I should like to ask Dr. Feder, who delivered the paper on liver biopsy, one or two questions. What did he do, if anything, in preparing for biopsy those patients who had prolonged prothrombin times? Secondly, did he have occasion to do biopsies on patients with diabetes and did they show a fatty liver cirrhosis? Thirdly, what was his technic in those cases where the liver was not enlarged?

Dr. Isidore A. Feder:—As for the prothrombin time, we always make the effort to correct it with Vitamin K. In instances, however, where it has not been possible to return the prothrombin time to normal, we have done liver biopsies without untoward effect. Thus, in Case R. G., the patient whom we biopsied annually in order to follow the evolution of cholangiolitic cirrhosis from cholangiolitic hepatitis, the biopsies were performed during her last two admissions when the prothrombin time ranged from 30 per cent to 40 per cent. Her platelet counts and bleeding times were normal. This has not been only our experience. Stefanini*, in his remarks concerning liver biopsy at a case discussion at the Massachusetts General Hospital, states, "I should like to say that the plasma prothrombin has limited importance in the selection of cases for liver or splenic biopsies. We have found that severe thrombocytopenia and a prolonged bleeding time are much more important contraindications to biopsy procedures than a prolonged plasma prothrombin time. In fact we have done biopsies in the presence of plasma prothrombin activity as low as 20 per cent without complications when platelet count and bleeding time were within normal limits."

We have not routinely done liver biopsies in diabetics with enlarged livers. In those which we have done, where the diabetes has been well controlled, the biopsy was normal. Where the diabetes was poorly controlled, and no other disease existed, our findings were those usually noted in such cases, namely, fatty infiltration and depletion of cytoplasmic glycogen. In the three diabetics who suffered from hemochromatosis, hemosiderin deposits and liver damage with cirrhotic changes were noted.

As a rule we follow the same technic for the patients with or without enlarged livers. As I stated before, the approach is through the eighth or ninth right intercostal space in the axillary line unless there is a transposition of the viscera when the same approach is made on the left side. On occasion, when we wish to enter a nodule on the anterior surface of the enlarged liver, we approach the nodule directly through the abdominal wall.

*Stefanini, M.: Case Records of the Massachusetts General Hospital (Case 41301), **253**:150, (28 July), 1955.

THERAPEUTIC CONSIDERATIONS IN ACUTE AND CHRONIC DISEASES OF THE LIVER*

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The treatment of liver disease, as that for any other disease, has for its objective the removal, if possible, of the causative factor, the amelioration of the presenting symptoms, the prevention of further damage and the repair of the already damaged parts, as soon as possible and by the simplest mode. Similarly, as in other diseases, in planning the therapy, one must consider the duration and stage of the disease, whether acute or chronic and its severity. Thus, a mild form of acute liver disease may require only little treatment outside of bed rest and a dietary regimen while a more severe case, whether acute or chronic, will require manifold therapeutic procedures. Similarly, once the disease has progressed to the stage of liver insufficiency or coma, the treatment, as used at present, is similar for both the acute or chronic forms. The only differences in the therapeutic regimen between the two forms are those related to the complications which may be present in chronic liver disease such as ascites and hemorrhage.

Based on observations in over 1,000 cases of liver disease, most of them seen in a large charity hospital and some in private practice, the following therapeutic principles can be presented as having proven their value during the past 15 years.

Rest

The patient with acute liver disease should be put to bed and kept in bed until the course of the disease is definitely on the upgrade as evidenced by clinical and laboratory data. Some types of liver disease, particularly those due to virus infection, appear to be very sensitive to physical exertion despite some recent observations to the contrary[1]. Rest in bed prevents jarring and massage of the liver and excessive metabolism of other tissues, the products of which, if themselves not toxic to the liver, have to be detoxified by it thus increasing the work of a damaged organ which may possibly be harmful. In some of these patients gradated activity and avoidance of excesses of any kind is indicated not only during the acute but even during the convalescent phase and extending for several months past the acute stage. If liver disease is associated with

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jaundice due to an extrahepatic factor, the need for prolonged rest is less mandatory.

Diet

Since, at present, we have no definite specific therapy for most of the liver diseases (except some specific ones, e.g. amebic hepatitis and tuberculous granulomata among others) the dietary regimen is important both in production, prevention and treatment of liver damage. While there are certain controversies concerning the need of some and the harmful effects of other food substances[2], all agree that a balanced diet is necessary in liver disease. In general it may be stated that the diet for a patient with liver disease should be high in calories, high in vitamins, average to high in proteins, high in carbohydrates and average in fat. There are, however, some instances of acute liver disease—e.g. toxic hepatitis in patients with fatty liver—in which the diet may have to be, for a variable length of time, rather low in calories and contain mostly carbohydrates with little protein and fat.

The diet should be comparatively bland, free of spices or condiments and low in salt. It should not be of extremes in temperature—too hot or too cold—and it should not contain any heated fats or soups with meat extracts[3]. It should be served to the patients in a pleasant, attractive way so as not to make them antagonistic to the dietary regimen. It is also preferable to serve several small feedings daily rather than just three meals.

Fats:—The amount of fat in the diet will have to vary according to the presenting condition and the patient's likes. In the acute cases particularly, the quantity of fat is of no great importance. The diet should contain enough fat to make palatable meals. It is far better to give the patients a diet which contains a few more grams of fat but which is palatable and completely eaten rather than to adhere strictly to a limited fat diet which the patient does not eat because it is non-palatable.

Fat of animal origin, excluding dairy fats, with their high contents of saturated fatty acid are particularly undesirable in liver patients, much more so after heating[4]. Since it is agreed that a fatty liver is a sick liver, one which is more susceptible to injury from endogenous or exogenous hepatotoxins[6], one must be careful to prevent the excessive accumulation of fat in the liver by a well regulated diet.

Carbohydrates:—Carbohydrates are given freely to patients with liver disease. Anywhere from 350-500 gm. daily are offered depending on the patient's ability for utilization. The urine should be watched for the appearance of glycosuria. If it appears, smaller amounts of carbohydrates at more frequent intervals may have to be given. If the patient cannot take the total amount orally, some of it may be given in the form of parenteral fluids. Carbohydrates which are easily digested and of low residue are preferable for patients with liver disease.

Proteins:—Patients with liver disease should get anywhere from 1 to 1½ gm. of protein per kg. The protein should be of high biologic value because only those proteins which contain all the amino acids necessary are useful for patients with liver disease. The value of the various amino acids in the body economy are at present well recognized. Deficiency of certain amino acids, besides the hypoproteinemia itself, may produce significant and dangerous changes in the body fluids, hormonal secretion and immunologic response. Adverse changes in the latter may in turn have an influence on liver metabolism. Some patients with chronic liver disease who are in a state of impending liver failure, do get along better if their diet is rather low in proteins. This would suggest that the patient's functional status should be carefully evaluated before ordering a therapeutic diet.

Vitamins

Despite the fact that the diet is high in vitamins, patients with liver disease should get additional vitamins by oral or parenteral routes. Studies have shown that Vitamin A is diminished in the plasma of acutely jaundiced patients even though the liver contains much Vitamin A[6]. In chronic liver disease however, Vitamin A is decreased both in the plasma and in the liver *per se*. In liver disease moreover, there is only a slight increase in the blood Vitamin A level following a given dose of oral Vitamin A. It is, therefore, important that patients with liver disease should receive large doses (50,000 to 100,000 U of Vitamin A orally) if in oil and one-half the amount of an aqueous solution in order to keep the blood Vitamin A level at a functional level. At present, Vitamin A is best given in the form of the aqueous solution. It can also be given parenterally if necessary in the form of Vitamin A palmitate in an aqueous dispersion. The need for Vitamin D can usually be covered with the administration of the average Vitamin A preparations.

The addition of extra amounts of Vitamin E in liver disease is at present a moot question although there are definite observations that the plasma Vitamin E is very low in some cases of liver disease[7]. Doses of 100-300 mg. of Tocopherol have been suggested for patients with liver disease.

Vitamin K is indicated only in those cases who have a low prothrombin time. Cases of severe liver disease with a very depressed prothrombin activity do not respond very readily to Vitamin K[8]. This vitamin should, however, be given in any patient with a low prothrombin level. If large doses of synthetic Vitamin K (72 mg.) do not show any improvement the K_1 preparations (Mephyton) should be used (50 mg. dose). The latter must be given intravenously in a solution prepared by mixing the 1 c.c. oily liquid K_1 with about 5-7 c.c. of a suitable aqueous diluent (water for injection USP or sterile isotonic sodium chloride solution) and injected slowly (10 c.c. in 1 minute). The emulsion may be added to infusions of dextrose and/or saline.

Vitamin C which is stored only little in the body, is readily depleted and therefore, large amounts should be given to patients with liver disease. Reports from abroad indicate that large doses of Vitamin C may be specific in some cases of liver disease[9]. We give patients at least 1,000 mg. of Vitamin C in addition to their intake in the diet, since it is supposed to influence favorably carbohydrate and protein metabolism and to prevent fat deposition.

The fractions of the Vitamin B-complex are very important in patients with liver disease. Although the need for thiamine hydrochloride, riboflavin, nicotinic acid and pyridoxine is present, other fractions seem to be also of importance. Folic acid, B_{12} and possibly some other as yet unknown substance appear to play a more important role than the above. Thus, Vitamin B_{12} has been reported by some as valuable in the treatment of hepatitis[10]. We, therefore, give our cases of liver disease, particularly those who are severely ill, large amounts of crude liver extract intramuscularly, because we believe that it represents the best form of giving the complete B-complex. Yeast powder is a less concentrated form of the B-complex. In some instances a "preparation of crude liver extract" can be used intravenously with good results[11].

Miscellaneous Procedures

Whenever the patient gets a supplemental protein drink, it should be given shortly after the meals rather than before the meal, since any of the supplemental foods decrease the appetite. Similarly, the patients who are not able to take their caloric requirement by mouth and who, therefore, get parenteral supplements, dextrose or solutions of amino acids, should be given these fluids after the evening meal, if at all possible. We try to give most of the supplemental fluids late in the afternoon or early evening so that the already finicky appetite of these patients may not be further decreased during the day. Parenteral fluids, especially protein hydrolysates give the patient a feeling of satiety. The latter, particularly, when given by fast drip may cause nausea and at times vomiting.

Not only the parenteral or oral food supplements but also most of the other medications which the patients are taking orally should be so arranged as not to come too close before their meals because it may interfere with their appetite for the food by causing nausea or a feeling of discomfort prior to the meal. Even the parenterally administered medication should be given at other times than immediately before or after meals so that patients are not upset as some of them get from a "needle" before their meal. Similarly any diagnostic procedures should not be done closely before or after a meal.

Medications

While there are no specific medications for liver disease there are a number of substances which do modify the course of liver diseases both during the acute

or chronic stage. It is obvious that in all patients who do have a liver disease due to some recognized hepatotoxic substance, the latter should be immediately stopped and antidotes if available should be administered. Thus, in patients with liver disease due to heavy metal poisoning Bal may be indicated. Calcium disodium versenate may be useful in liver disease associated with lead intoxication.

Antibiotics:—Any patient with liver disease who has a fever should have an antibiotic. The best antibiotics for a patient with liver disease are those of the broad spectrum type, despite the feeling by some that a broad spectrum antibiotic may cause fatty changes in the liver[12]. These latter occur only after very large doses, are comparatively slight and disappear after the medication is stopped. On the other hand, we have had good therapeutic results following these antibiotics in many very ill patients[13]. Recent observations by Sherlock and her co-workers have apparently explained the basis for the good results with this antibiotic[14] through its effect on the B-coli.

Sedatives and analgesics:—Many patients with liver disease need intermittent or constant sedation for one or the other reason. Opium derivatives as a rule are contraindicated although small doses of codeine may be given. Demerol may be used as the narcotic of choice. The long acting barbiturates (phenobarbital or barbital) are preferable to the shorter acting ones (nembutal and seconal) which are mainly excreted by the liver. Chloralhydrate is preferable to paraldehyde. It must be kept in mind, however, that any sedative or narcotic substance should be given in smaller dosage to patients with liver disease than would be given to patients of a similar age group but without liver disease. In patients with liver disease due to chronic alcoholism, 5 per cent alcohol solution in dextrose given as venoclysis serves as an excellent sedative during an acute exacerbation with or without delirium tremens thus obviating the need for paraldehyde. If an anesthetic becomes necessary, cyclopropane is the anesthetic of choice[15]. Salicylates in the form of sodium salicylate or acetylsalicylic acid are apparently well tolerated and may be given freely.

Recently Sparine has been found very useful in quieting disturbed patients with liver diseases.

Antipruritics:—Patients with chronic liver disease frequently complain of severe pruritus. No specific substance is as yet known which relieves pruritus satisfactorily. Acetylsalicylic acid, ergotamine, antihistaminics and cortisone may have some beneficial effect. The best results at present are obtained by procaine in 0.1 per cent or 0.2 per cent solution given as venoclysis in saline or 5 per cent glucose. Occasionally drainage of the common duct must be resorted to for relief of pruritus even in cases of nonsurgical jaundice.

Calcium:—In some patients with acute liver disease, especially with severe jaundice, calcium gluconate in doses of 10-20 c.c. of a 10 per cent solution given

two or three times daily appears to have a beneficial effect. The theoretical basis for the use of calcium is that this substance neutralizes some hepatotoxins (guanidine and related compounds) which accumulate in the blood during severe liver disease[16].

Laxatives:—Many patients with liver disease complain of severe constipation. A mild saline laxative, or one of the substances of the phenolphtalein or anthraquinone group may be useful if given in small doses nightly.

Digestants:—In patients with chronic liver disease particularly, flatulence, belching, and abdominal discomfort is frequently met in addition to anorexia and nausea. In these patients some relief may occasionally be obtained by the judicious use of dilute hydrochloric acid and bile salts with or without a mixture of pancreatic substance.

Diuretics:—Patients with chronic liver disease are apt to have edema and ascites. These patients do not respond as readily to mercurial diuretics as do cardiac patients. Nevertheless, mercurial diuretics have a place in the treatment of these patients. While the efficacy of ammonium chloride as an adjuvant to the diuretic effect of mercurials has been controversial, there is at present no controversy as to the use of ammonium chloride in patients with chronic liver disease. In the latter, *it should not be used at any time*, because ammonium salts may cause the patients to go into a drowsy stage or actual coma as has been observed by workers in this field[17]. Nonmercurial diuretics may be tried when mercurial substances fail to produce diuresis. The new diuretic Diamox should not be used in cases with chronic liver disease since it has a tendency to raise the serum ammonia level, just like ammonia salts. Whenever mercurials are given for diuresis, one must make sure that there is no hypochloremia, since if the plasma chlorides are low there is no diuretic effect. Some patients may require, additionally, hypertonic dextrose solution or dehydrochloric acid (Decholin®) for enhancing the diuretic effect of any of the above substances.

Electrolytes:—Patients with severe liver disease either during the acute or chronic stage, should have careful check of their electrolytes because electrolyte imbalance is not uncommon. Deficiencies in potassium and magnesium are frequently found.

Testosterone:—Some patients with chronic liver disease with persistent negative nitrogen balance show occasionally improvement in their appetite and general condition upon the injection of testosterone[18]. This substance apparently has an anabolic effect and while its basis is not quite established, it is worthwhile to be given a clinical trial in a patient who fails to respond to other treatment.

Steroids:—In the last few years a number of controversial papers have appeared about the effect of steroids in liver disease[19]. In our clinic we have used steroids (ACTH and cortisone) mainly in severely ill patients, both in the

acute and chronic stage. It is our impression that in some instances steroids do change the course of the disease in a favorable direction. We use ACTH intravenously by the slow drip, giving approximately 20 units of ACTH per thousand c.c. of glucose and water. Cortisone we usually give parenterally every 6 or 12 hours. In patients who are severely sick or precomatous up to 400 mg. daily is given for the first 24 hours reducing it then to 200 mg. a day for several days and then decreasing to 100 mg. or less. Whole adrenal extract has been given to some patients with chronic liver disease but with only equivocal results. It is possible that these substances act mainly as nonspecific agents by helping detoxification, increasing the appetite and general feeling of well being.

Crude liver:—We give crude liver to patients with chronic liver disease particularly, or to the very sick with acute liver disease because of the feeling that it may contain some useful factors which have as yet not been isolated, but which are useful for a damaged liver. Crude liver seems to improve the patients' appetite and helps some by an increased diuresis.

Salt substitutes:—Most patients with acute or chronic liver disease have to be on a low salt diet. Since many patients do not like tasteless food, it is imperative that for some of them one or the other of the salt substitutes should be prescribed. The latter helps the patients to adhere to their salt free diet.

Glutamic acid:—In the past several years reports about the efficacy of glutamic acid in the treatment of hepatic coma have appeared[20]. Unfortunately, our group has not been able to confirm these reports, in a number of patients with hepatic coma. Thus, of 20 cases with hepatic coma in whom glutamic acid was used, only one patient recovered and has survived for over one year. Several patients who at first seemed to show a favorable response to the glutamic acid infusions had a relapse several days after the glutamic acid was stopped, and died. Because it is possible that our material consisted of very severe and late cases, we feel that glutamic acid therapy should be continued, so that observations on a larger series may be obtained.

Thioctic acid:—In recent months a new substance (Thioctin) was reported as promising in the treatment of liver disease[21]. This substance too, has in our hands to date not shown any remarkable beneficial results.

Lipotropic substances:—In some cases of chronic liver disease, particularly those associated with a large, fatty liver, lipotropic substances may be of value by helping in the transport of excess fat[22]. While there is no definite proof that these substances have a specific effect, nevertheless, clinical observations seem to indicate that they have some beneficial results in patients thus treated. In acute liver disease the beneficial effect of their use has been reported only in cases of toxic hepatitis associated with fatty infiltration[23].

Fluids:—During the acute illness and also in the more chronic cases signs of water retention demand a restriction of fluid intake. As a rule we find that

patients do not mind if their fluids are restricted to 1,200 or 1,500 c.c. daily. More severe restrictions are not readily tolerated.

Alcohol

The use of alcoholic beverages should be prohibited in patients with both acute and chronic liver disease. In the latter it should be prohibited at all times.

Complications

Chronic liver disease is frequently associated with ascites and bleeding.

Ascites:—The appearance of ascites in a patient with liver disease presents an additional disturbing factor because it indicates further advance of the disease. While there are a number of factors possible for the development of ascites, several of them are at present considered most important. One is the hypoalbuminemia; the second is the salt retention; the third is the possible increase of the antidiuretic factor; and fourth is the disturbance in the vascular bed of the liver. The patient who develops ascites may develop edema in addition. The presence of ascites creates additional difficulties for these patients concerning the intake of food and fluids and may at times also cause respiratory difficulty. Frequently, strict restriction of the salt intake, limitation of fluids and the administration of diuretics may somewhat decrease the ascites. At times (when the patient is anemic) the administration of blood may help. Salt-free human albumin has been used with occasionally good results[24]. In general it may be stated that we try all types of measures first before we resort to abdominal paracenteses.

Bleeding from the gastrointestinal tract:—Many patients with chronic liver disease have at times hematemesis or melena. A small hemorrhage can be treated simply by blood transfusion. If, however, the hemorrhage is more profuse a Sengstaken tube may have to be used for compression of the varicosities in the lower esophagus and/or cardiac end of the stomach. A surgical approach to bleeding varicosities by ligation of the blood vessels and other surgical measures as recommended by some[25], has not been used on our patients.

Coma:—The end result in many cases of chronic liver disease is hepatic insufficiency or coma. In these patients we use large amounts of dextrose intravenously (5 or 10 per cent) by almost continuous infusion, keeping in mind to keep the electrolytes balanced and the fluids within physiological limits. We give the patients large doses of ascorbic acid, thiamine hydrochloride, riboflavin and nicotinic acid in addition to crude liver intramuscularly or intravenously. Occasionally hypertonic glucose solutions are given if the amount of fluid is to be kept down. If the patient is anemic we give small blood transfusions daily or every other day. We also use oxygen on patients who are comatous inasmuch

as the liver is very sensitive to anoxia. The use of glutamic or thioctic acid and of steroids and antibiotics in patients with coma has been referred to above.

Surgical Therapy

In some cases of chronic liver disease, particularly with persistent jaundice, surgical decompression of the ductal system of the liver may be a valuable procedure[26]. While the basis for the improvement following such a decompression is at present unknown, experiences with this procedure in a small number of cases have been favorable enough to warrant its consideration in an occasional patient.

General Treatment

Patients who suffer from chronic liver disease should be carefully watched for any other abnormal conditions which may aggravate the primary liver disease. Any deviation from normal in the other body systems (respiratory, cardiovascular, renal) should be adequately treated so as to prevent additional loads on the diseased liver.

Conclusion

A review of the various procedures in acute or chronic liver disease is presented and some of the bases for these procedures are discussed. In general, it is felt that in patients with liver disease good nursing care and supportive treatment are the main factors which may help the patient, since no specific substance has as yet been found. Under supportive treatment we include a rational adequate diet, proper amounts and types of fluids, balanced electrolytes, and adequate use of antibiotics, steroids, blood, oxygen and other medications which may favorably influence the impaired functional and structural state of the liver.

I wish herewith, to express my thanks to my many co-workers in the liver group who have helped me in this work during these past years.

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FUNCTIONAL BEHAVIOR OF THE PANCREAS*

A Study of its Relationship to Chronic Diseases

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and

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Introduction

Pancreatic function presents a complexity. Proper analysis of almost any ramification of dysfunction would occupy full space allotted to one report. This report will cover only the phase related to carbohydrate metabolism. We hope to report later on other phases of the study. Our objective was to determine if a hidden functional misbehavior of the gland could cause or contribute to certain clinical abnormalities obscure in exact etiology, resistant to known treatment, and not conventionally considered as being related to the pancreas. Blood sugar behavior curves can be classified into patterns, and these zones applied to the clinical symptoms of the cases observed.

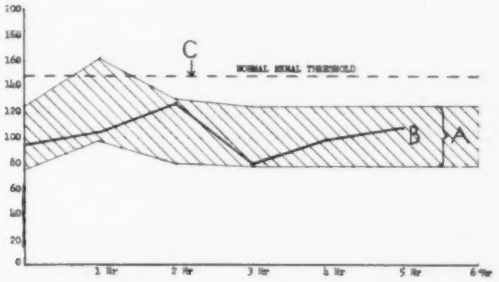

Fig. 1—Basic 6-hour glucose tolerance zones: A. Zone derived from 50 Normals. B. Patient curve falling within normal zone. C. Normal theshold (renal).

The end results, admittedly, are complicated, and technically may be claimed somewhat inconclusive; but definitely they are considered worth reporting from a viewpoint of potential clinical significance and to stimulate further study.

Carbohydrate metabolism, as related to the pancreas, is well established at points of two extremes; namely, hypoinsulinism and hyperinsulinism. In both there are still problems unsolved. We believe that our observations indicate the presence of a "twilight zone" in which either or both can exist and con-

*Read before the Second Annual Convention of the American College of Gastroenterology, Chicago, Ill., 24, 25, 26 October 1955.

tribute to some of these obscure clinical problems. In other words, our studies indicate that both hyperinsulinism and hypoinsulinism may exist in the same case, and such cases may refuse to assume a conventional pattern of either diabetes or true hyperinsulinism. Even though somewhat irrelevant, it is valuable to note that modern endocrinology is following this same concept relative to thyroid function. When this concept was applied to certain intractable diseases, a striking relationship to pancreatic function was observed.

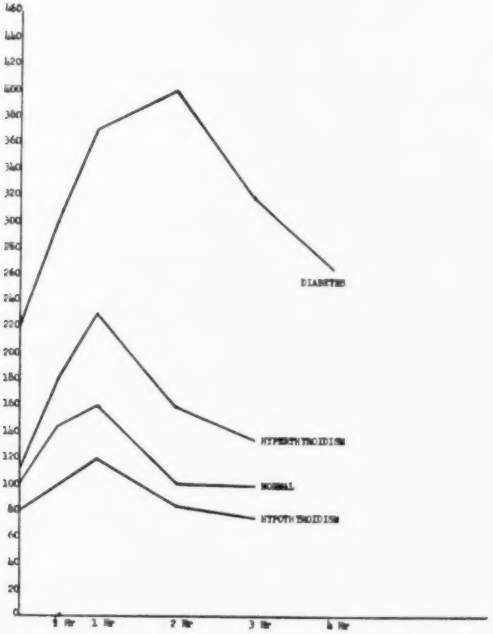

Fig. 2—Accepted curves for normal, diabetes and thyroid disturbances, under glucose tolerance tests.

Method of Study

The studies have covered a total of 1,060 cases and extend over a period of 17 years.

Six-hour glucose tolerance curves were selected as a laboratory guide to establish pancreatic function in relation to carbohydrate metabolism. Separate fasting and postprandial blood sugars, prior to the tolerance test, were carried out in all of the early and many of the later cases, as a testing device to observe any value they may have as a countercheck to curves revealed by the tolerance tests.

Other pancreatic functional studies and calcium determinations were made, but cannot be included within space allotted this report. It is essential, however, to emphasize that in those revealing a hyperinsulin zone, there is a constant tendency toward a lowered calcium utilization level. The significance of this emphasis will be discussed under treatment.

Fifty of the cases, considered clinically normal, were subjected to the carbohydrate test routines to establish what we feel is a normal "reaction zone". This, together with renal threshold average, is presented in Fig. 1.

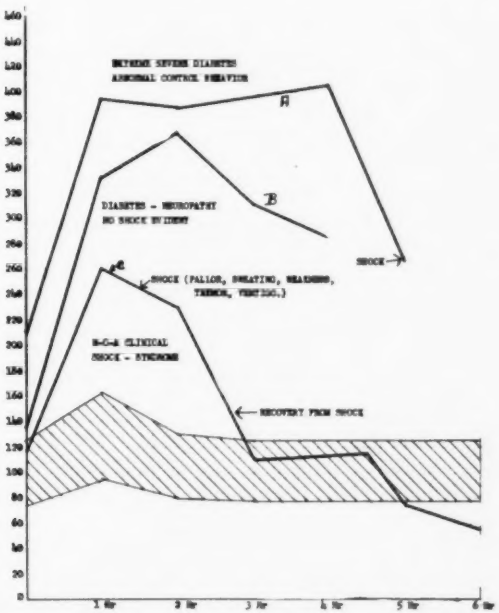

Fig. 3—Glucose tolerance curves from 3 patients. A. and B., Severe diabetes both erratic to control by usual treatment: Note shock in A. C., N-C-A, clinical syndrome showing both hyper- and hypoglycemic responses in same patient. Note shock reproduction, even at different sugar levels.

The balance of the cases were made up of groups selected from a number of obscure clinical conditions commonly met in practice. They include arthritis, allergy (with or without diabetes), essential hypertension, functional gastro-enteropathies, multiple sclerosis, and a vague but realistic type of clinical syndrome becoming more prevalent, currently identified under several descriptions, probably not commonly called neurocirculatory asthenia, abbreviated in the tables N-C-A.

These groups have been carefully studied relative to history and physical examination including routine laboratory tests. They were then subjected to the routine sugar tests, and finally critically analyzed to decide if any interrelationship existed between the clinical syndrome and pancreatic functional behavior. These cases showing pancreatic misbehavior curves were subjected to a routine treatment devised and a final observation made of symptomatic results. Cure is not used because we feel that in these diseases, a cure is always controversial.

Data and Results Obtained

In the final analysis, concentrated over the past 10 years, some two-thirds of the total cases observed had to be eliminated. This was due to unexplained discrepancies which rendered interpretation inconclusive. This left, not including the normals, a net of 300 cases which we feel are rigidly screened and do conclusively represent the objective. Figure 1 represents the control zone estab-

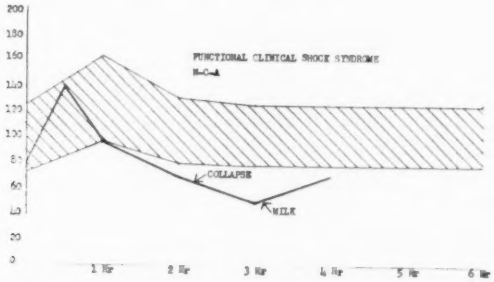

Fig. 4—Illustrating patient with typical hyperinsulinism. Note shock in this case occurred at low sugar level, and recovery followed milk.

lished in the 50 normals subjected to six-hour glucose tolerance tests. Table I is constructed to reveal the definite relationship between the glucose tolerance behavior and certain clinical conditions. Table II projects the clinical results obtained when the cases, from each group showing either frank hypoglycemic or twilight zone (midzone) reactions, were placed on the established treatment. Figure 2 is, to recollect for the reader, the contour of commonly established glucose tolerance curves. Figure 3 demonstrates the beginning of our objective, a complicated, though significant, problem to unravel. Here are three cases, all of which by standard two- or three-hour tolerance tests could have logically been dismissed as diabetes of variable severity. Two of them (A and B) were diabetics, but were totally erratic in behavior to treatment control. The third (C) was not diabetic at all; but was a case selected from the group presenting the complicated clinical pattern (termed N-C-A) and his presenting symptoms were paroxysms of vertigo, pallor, sweating, palpitation and extreme fatigue. More puzzling is an attempt to interpret the physiological mechanics

involved when the clinical complaint was actually reproduced during the tolerance test. For brevity we have called this "shock". In both A and C the shock reaction occurred at distinctly different points in the individual behavior curves. Furthermore, while case C spontaneously recovered as the tolerance sugar level fell, Figure 4 demonstrated "shock" and collapsed at a low level, recovering rather rapidly with a concomitant rise in sugar level following administration

TABLE I

ILLUSTRATING A DEFINITE RATIO BETWEEN HYPOGLYCEMIA AND SEVERAL IDIOPATHIC DISEASES.

Cases	Age	Sex	Primary Clinical Complaint	Glucose Tolerance 6 Hours
54	27-89	M–18 F–36	Arthritis: Rheumatoid and Osteo, Neuromuscular.	11 Hypo Zone (All under age 65) 3 Diabetic 40 Within Normal
59 1	12-73	M–27 F–32	Allergy-Rhinitis-Asthma. Asthma plus diabetes.	19 Hypo Zone (All under age 60) 41 Normal
32	48-63	M–20 F–12	Hypertension–Idiopathic.	5 Hypo Zone (All females) 27 Normal
60	42-89	M–25 F–35	Functional Gastrointestinal Syndrome: Hunger distress-Gas-Bowel upset.	45 Hypo Zone 15 Normal
4	32-56	M–1 F–3	Multiple sclerosis.	4 Hypo Zone–All improved under therapy.
90	32-61	M–70 F–20	N-C-A Shock Syndrome: Sweating-Weakness-Pallor-etc.	30 Hypo Zone (Both sexes) 40 Normal 20 Twilight Zone

300 Total Cases.

of a large quantity of milk. Our present physiological concepts of pancreatic functional behavior do not explain these patterns. This case (Fig. 4) by her glucose tolerance curve is a typical example of hyperinsulinism; but Figures 5 or 6 will not fit that pattern. A "twilight zone" apparently exists and can only be detected by tolerance curves of 4 to 6 hours. Both nasal and gastrointestinal allergy exploded during the test. Figure 6 demonstrates another type of "twilight

zone" tolerance curve. The severe N-C-A symptoms of weakness, sweating, pallor, etc., responded well to the standard treatment.

In summary, the results tend to confirm a hypothesis; namely, that both twilight and advanced zones of pancreatic dysfunction, detected by 5 to 6 hour tolerance curves, can be contributory to the etiology of some obscure diseases. The proof is first, reproduction of the symptoms during the test, and secondly, the improvement of the symptoms by a uniform treatment.

Treatment Program

We established a standard therapeutic regimen aimed at three fundamentals. 1. To lessen insulin production of the pancreas; 2. Supply diffusible calcium adequately, and 3. Elevate threshold irritability of the autonomic nervous system.

Diet is of primary importance. Harris[3], Abrahamson and Pezet[1], Portis[4], and others have long since established that concentrated sugars produce ex-

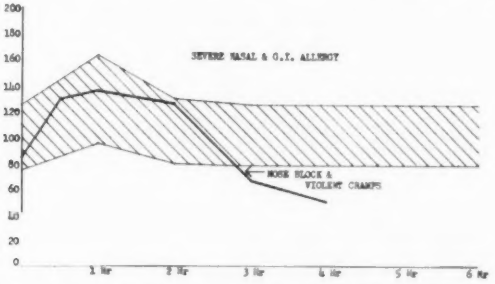

Fig. 5—Glucose tolerance curve in case of severe allergy. Note reproduction of the symptoms at the hypo level.

cessive pancreatic stimulation. Concentrated sugars are eliminated from the diet in the beginning, later restricted. Fats depress sugar tolerance levels and are given adequately. Detailed diet lists are presented in the writings of the above authors. We agree with Abrahamson that hunger contractions aggravate, and they are controlled by between meal feedings. Our studies also confirm his, that fasting sugar determinations are not diagnostically correct; and post-prandial levels are more physiologic.

We believe a low calcium utilization level exists in these cases even though blood levels are usually not very low. Oral calcium is given routinely, but the supply is additionally fortified with intramuscular injections of a double calcium and phosphate salt (Calphosan-Carlton Corp., N. Y. C.) which works well and is free from local reaction. Kurtz[5] has reported the value of this salt in allergy.

Control of autonomic irritability is more problematical. The condition exists in most of the cases. Gastrointestinal spasm is likewise predominant. Our best results have been with employment of a product combining synergistic action between a belladonna derivative and phenobarbital under the newly "sustained action" process of drug release (Spasticol S. A.—Key Corp., Miami, Fla.). This pharmacological sustained action is not to be confused with presently understood delayed action.

TABLE II

RESULTS OBTAINED BY ROUTINE TREATMENT (DIET-CALCIUM-AUTONOMIC BALANCE) IN DISEASES WHICH ALSO PRESENT HYPOGLYCEMIC PATTERN

Cases	Clinical Complaint	Glucose Tolerance Status	Treatment (Routine-Diet-Calcium-Spasticol S.A.)	None	Mod.	Good
11	Arthritis: 7 Rheum. 4 Osteo.	Hypo Zone	Routine	1	2	8
18	Allergy: 10 Mixed 8 Asthma	Hypo Zone	Routine plus symptomatic	4	4	10
5	Hypertension—Idiopathic	3 Hypo 2 Mid Zone	Routine but other B.P. drugs withheld	—	1	4
45	Functional and Allergic G.I. Syndrome	Hypo Zone	Routine plus digestant	7	8	30
4	Multiple Sclerosis	Hypo Zone	Routine plus Physical Therapy and Histamine	—	—	4
50	N-C-A Functional Shock Syndrome	30 Hypo 20 Mid-Zone	Routine	10	15	25

133 Total Cases Treated.

Clinical benefit by this regimen has been gratifying beyond doubt.

GENERAL DISCUSSION

Admittedly, several problems are presented and unsolved. This in no way detracts from the stimulative value of the results obtained by the study. The fact that we have reproduced the primary presenting clinical complaint by

shocking the pancreas with an overload of glucose (Figs. 3, 4, 5) and the complaints improved under our established treatment—Table II (primarily aimed at the pancreas) proves a significance. Current clinical knowledge cannot explain some of these patterns, but we believe future physiologic study will do so.

The normal glucose tolerance zone, established by us, cannot be radically wrong, since other workers have established curves almost identical[1]. If this be true, then the balance of our graphic patterns represent abnormal behavior. We cannot actually prove this misbehavior of the pancreas caused any of the diseases tabulated, but certainly symptomatic improvement ensued when pancreatic treatment was instituted. Emphatically important is that this held true regardless of the primary disease treated, only when the case fell within the twilight or hypo zone. Review of the figures will again reiterate that many such cases will be missed unless 4- to 6-hour tolerance analysis is set up as a standard.

Definite attention is called to the four cases of multiple sclerosis (Tables I and II). Abrahamson[2] has reported 126 cases falling within this pattern.

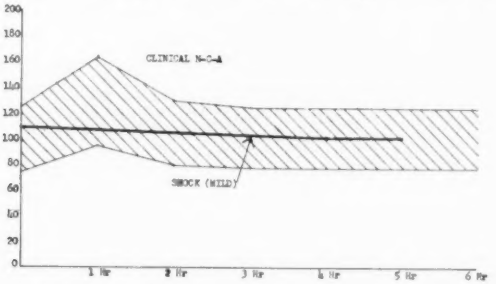

Fig. 6—"Twilight zone" glucose tolerance curve. Patient presented severe N-C-A clinical syndrome, shock reproduced during test, definite recovery from symptoms with routine management.

Gastroenterologists cannot sit immune to this problem, because pancreatic function is one of their constant responsibilities. Furthermore, one of the only reliable physical signs to indicate the condition is a tenderness over the region of the tail of the pancreas. Seale Harris has emphasized this point. Table I shows 60 cases where gastrointestinal symptoms were the presenting complaint. There are other questions which our study fails to answer. Is the pancreas primarily out of function, or is its misbehavior secondary to an abnormal impact by other endocrine disturbance or autonomic nervous system imbalance? Clinically the N-C-A group presents a symptomatic picture, during their paroxysms, not unlike adrenal dysfunction including pheochromocytoma. Accepted confirmatory tests rule this out technically, but still when adrenal stimulating factors are introduced they can, and often do, produce an observable aggravating response. A very definite majority of these cases, and regardless of the diagnostic complaint, demonstrate an autonomic nervous system instability. Portis[4] has

studied this at length. Undoubtedly, this could secondarily reflect its influence on pancreatic function; but why then, would the patient improve under therapy aimed only at the pancreas? We must admit that even after 30 years of insulin experience, we still have not solved its entire physiologic role. Controversies regarding compatible hyperglycemia still exist[6].

Some cases reveal true hyperinsulinism curves; but others, equally violent in clinical symptoms, fall only in the twilight zone. Patients with such flat curves (Fig. 6), however, are without doubt clinically hypoglycemic reactors.

From a therapeutic viewpoint these studies are significant. The diseases observed are increasingly common to all physicians, especially the N-C-A syndrome. Conventional treatment has not proven sufficiently satisfactory, and further study is indicated.

Conclusions

1. A method of determining pancreatic behavior relative to carbohydrate metabolism has been demonstrated.

2. A relationship between pancreatic misbehavior in this respect, and certain obscure diseases is indicated.

3. Principles of therapeutic regimen have been summarized.

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ACUTE HEMORRHAGIC PANCREATITIS, COMPLICATING BILIARY TRACT SURGERY*

Report of Two Fatal Cases

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Acute hemorrhagic pancreatitis with its sequelae, is fortunately a rare complication of biliary tract surgery. It may occur, however, more often than reports indicate, and it can be rapidly fatal, in spite of supportive therapy including massive doses of antibiotics.

Brown[1] has pointed out that "the pancreas is a labile organ which can be injured at operation, and acute pancreatitis may result from blunt trauma."

Hayden[2] refers to three fatal cases, secondary to this complication, reported by Pattison and Blatherwick, as well as two of his own, which fortunately recovered after a prolonged convalescence. He is of the opinion that, "It is probable that manipulation of, or trauma to, the ampulla or pancreas rather than any particular operation or apparatus is responsible for this uncommon complication."

A review of our records for the last ten years at St. Agnes Hospital (150 beds) shows a total of 411 cholecystectomies. Of this number 23 per cent had common duct drainage. We have always entertained a wholesome respect for the latter structure, exploration not being done unless definitely indicated, and then with care. In dilating the ampulla, no effort is made to introduce a bougie that the common duct will not comfortably accommodate. We have also made it a practice to culture each duct when opened.

The usual caution is also observed to avoid forcible passage of the bougie through the ampulla so as not to traumatize this structure or the head of the pancreas. Following evacuation of the duct contents it is irrigated with saline and T-tube drainage instituted.

The two cases herewith reported and the only ones we have observed (both mine), peculiarly occurred within three months of each other.

Case 1:—Mrs. H. C., age 73, was admitted to St. Agnes Hospital, 14 April, 1953, by her physician, because of occasional attacks of pain in the upper right quadrant of the abdomen, referred to the right scapular region and accompanied by nausea and vomiting. These attacks began about two years previously and occurred every two to three months. She had never been jaundiced.

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Eight years previously I had done a cholecystectomy, removing a large gallbladder, with thickened walls and containing numerous large and small calculi. Careful examination at that time of the common duct, and head of the pancreas indicated no abnormality. Her recovery was uneventful.

Prior to her second admission, she had not lost weight, her appetite was good, and bowels regular. The attacks lasted two to three days. There were no chills and fever.

Examination revealed a healthy appearing white female apparently as of stated age, and was essentially negative with the exception of some tenderness in the right hypochondrium. Here there was slight spasticity, but no masses were palpable throughout the abdomen. Heart sounds were normal and blood pressure 160/95. Reflexes were normal.

The diagnosis on admission was: 1. subacute pancreatitis; 2. duodenal ulcer. The urine was normal and the blood count within normal limits. The acid values were slightly elevated, and bile was present. The serum amylase was slightly elevated. At that time we were using the Bray test with a normal range of 40 to 120.

A stomach film from a gastrointestinal series, merely showed an extensive defect secondary to postoperative adhesions.

We no longer regard a gastric Papanicolaou of value unless the corded balloon is used.

Operation was done 29 April 1953 under general anesthesia, through an upper midline incision. Numerous dense adhesions were found in the upper right quadrant, between the under surface of the liver, pyloric end of the stomach, duodenum, and hepatic flexure.

The common duct was enormously distended, approximately the diameter of the duodenum. It contained a large amount of inspissated bile together with a large calculus wedged in the ampulla of Vater as well as many minute calculi. No abnormality of the head of the pancreas was observed.

The duct was opened, a culture made, and contents evacuated. Following this the ampulla was easily and gently dilated up to bougie No. 11, and irrigated with saline. A T-tube was then sutured into the duct with fine chromic catgut, a Penrose drain placed at the foramen of Winslow, both being brought through a stab wound in the right abdominal wall.

Her immediate postoperative condition was very satisfactory.

The culture from the bile duct revealed *B. Aerogenes.*

Combiotic therapy was instituted prophylactically immediately postoperatively. The Levin tube which had been inserted prior to surgery, was removed 30 hours postoperatively. Her condition that day was satisfactory with the ex-

ception of some nausea. There was, however, no vomiting or distention. She had little pain in the operative area. A moderate amount of biliary drainage was noted on the dressings, and that through the T-tube was normal in character. She was allowed to dangle her legs over the bedside and began taking water, ginger ale and broth in limited quantities without distention or nausea. There was no cough or dyspnea.

Dressings were changed again 48 hours postoperatively. The wound was clean, and T-tube drainage of bile was normal in amount and character. She was helped out of bed a few hours later, and while seated in a chair, about ten minutes thereafter, suddenly showed signs of profound shock. She developed marked pallor, dyspnea, tachycardia and the blood pressure was unobtainable. She complained of pain in the lower anterior left chest. There was no cough. The chest pain was not referred to the shoulder or either arm. An electrocardiagram was reported as within normal limits.

She was placed in oxygen and supportive therapy instituted. To supplement the combiotic she had been receiving, intravenous aureomycin was begun 500 mg. every six hours. Her blood pressure returned to 120/70, the color improved, her pain subsided considerably, but the pulse remained accelerated. She remained very alert mentally.

Intravenous fluids and electrolytes were given cautiously together with 500 c.c. of blood. The extremities remained rather cold and clammy, but there was no cyanosis. An x-ray of the chest was interpreted as showing clouding and probably atalectasis. She expressed a desire for ginger ale and suddenly expired 76 hours postoperatively, her temperature rising steadily to 105°F.

A chest x-ray was made about 24 hours prior to death. The left chest contained about 1,000 c.c. of thin cloudy purulent material, the left lung showing atalectasis.

A postmortem was done. The T-tube in the common duct was in position and clear of inspissated material. One small residual stone was in the lower common duct. The entire head of the pancreas was involved in a marked hemorrhagic pancreatitis, the body and tail not being involved.

The bilateral chronic nephritis was probably not a factor in her death. The mucus plug found in the left bronchus was not of sufficient diameter to occlude this structure, nor was it attached to its walls. It was my opinion that a spontaneous pneumothorax had occurred secondary to a pleural perforation. The microscopic diagnoses are apparent from this slide. It is quite evident she had an overwhelming blood stream infection which failed to respond to antibiotic therapy.

This is emphasized by cultures of the fluid found in the left chest and base of left lung, *B. Aerogenes* which was also cultured from the common duct at operation.

Hemorrhagic pancreatitis was limited to the head of this structure, and could well have been traumatic in origin, indeed a probable source of her septicemia.

There was obvious cholangitis, some of the lesions possibly existing preoperatively. Pleuritis, secondary to the sepsis in the left chest, was also present. Glomerulonephritis was apparent, and in all likelihood did not exist, certainly to this degree preoperatively.

Case 2:—Mrs. M. K., white, female, age 48, admitted to the hospital 26 July 1953 with a diagnosis of chronic cholecystitis and lithiasis, and choledocholithiasis. She had been told that she had cholecystitis since her youth. I had operated upon her in March of 1951 for acute suppurative appendicitis. Her recovery was uneventful. Her present illness started on 30 June 1953, with sharp pain in the upper right quadrant referred to the scapular region and accompanied by nausea. On 3 July, a gallbladder series showed a poorly functioning gallbladder with multiple calculi.

She was placed on a medical regime by her physician for three weeks, during which time she lost 15 lbs. The pain did not reappear.

On admission examination was essentially negative with the exception of a moderate amount of obesity. There was but slight tenderness in the upper right quadrant and no spasticity.

Urinalysis, specific gravity 1.012 and showing only a faint trace of albumin. Blood count 3,651,000 red cells, whites 5,100, a normal differential and hemoglobin 10.4 gm. Blood pressure was 100/65.

At operation 27 July 1953 a greatly distended gallbladder was found with a considerably thickened wall, containing innumerable small calculi, many of which were wedged in the cystic duct. There were dense adhesions between this structure, the omentum and duodenum. The common duct was slightly distended, the wall somewhat thickened and containing two small calculi wedged in the ampulla. The pancreas was palpably normal.

Following a cholecystectomy, the common duct was explored, stones removed and irrigated with saline. The ampulla was then dilated with ease up to bougie No. 4. A T-tube was then sutured into the common duct using four interrupted triple 0 chromic catgut sutures. A Penrose drain was placed to the foramen of Winslow, this and the T-tube being brought out through a stab wound in the lateral abdominal wall. Her immediate postoperative condition was very satisfactory.

On the first two postoperative days there was an exceptional amount of nausea without any other signs. Biliary drainage was satisfactory and the bowels moved in response to an enema. The operative area was apparently healing without evidence of infection, although there was moderate tempera-

ture elevation. Dramamine was given for the nausea. On the third postoperative day she complained of gas pain, but was retaining fluids by mouth. She had been on penicillin therapy since operation.

Also late on the third postoperative day, her temperature which had returned to normal, rapidly rose to 103°. Dihydrostreptomycin therapy was begun followed by intravenous aureomycin. There was still no distention or vomiting. Intravenous fluids and electrolytes were administered as indicated. The serum bilrubin was 1.0 and direct reaction was immediate. On the fourth postoperative day jaundice developed which gradually deepened. On the sixth day the blood pressure dropped to 88/70. The hematocrit was 33 per cent and hemoglobin 11.15 gm. She was transfused.

In spite of supportive therapy, her condition gradually deteriorated, she became comatose and expired on the eighth postoperative day.

At autopsy the gross anatomic diagnoses were: 1. Cholangitis; 2. Generalized peritonitis; 3. Massive retroperitoneal hematoma, occupying the entire right gutter; 4. Nephrosis and 5. Infected pulmonary infarct.

Microscopic diagnoses: 1. Cholangitis; 2. Hemorrhagic pancreatitis with fat necrosis; 3. Toxic nephrosis and 4. Septic infarcts with fibrinous pleuritis.

Various cultures showed: On 4 August 1954, Urine—Enterococci and *B. Aerogenes*. On 6 August 1954—Culture of autopsy showed enterococci in the common duct right lumbar gutter; peritoneum; right pleura.

Hemorrhagic pancreatitis and fat necrosis were present.

There was necrosis of the inferior pancreatico-duodenal artery, which in the opinion of the pathologist accounted for the large hematoma in the right gutter.

Comment

Both of these cases developing this devastating complication, occurred within a few months of each other, and were the first I have knowingly had, in my experience following choledochostomy. A review of the literature indicates its comparative rarity, although it may occasionally go unrecognized. Brown reported "A Mayo clinic series showed twenty deaths of 1,261 biliary operations and only one due to acute pancreatitis."

MacKenzie has reported, "recently the role of surgery as the etiological agent in this disease has been stressed." In his series, two fatal cases "followed choledochostomy with considerable manipulation in the region of the ampulla."

Madden at the meeting of the American College of Surgeons at Atlantic City, November 1954, in describing his technic of biliary tract surgery, stated

he rarely introduced a bougie into the common duct, larger than a No. 4. It would seem logical that coexisting infection and trauma are the precipitating factors in this complication.

Summary

Two fatal cases of acute pancreatitis complicating choledochostomy are reported. The rarity of this condition is stressed, and should be suspected following biliary tract surgery in the event of severe epigastric pain, nausea and vomiting, and if diagnosed, treated heroically.

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INFLAMMATORY DISEASES OF THE PANCREAS*

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General Considerations and Physiology

The pancreas is one of the smallest and most deeply placed organs in the abdominal cavity. It lies transversely in the epigastrium crossing the bodies of the 12th thoracic and first lumbar vertebrae. It extends from the curve of the first part of the duodenum to which it is firmly attached, to the hilum of the spleen.

Physiologically, the pancreas plays a double role, endocrine (carbohydrate metabolism) and secretory (digestive).

The *external secretion* is produced by the alveolar tissue. This reaches the duodenum via the ductal system of the pancreas. Fifteen hundred to 2,000 c.c. are secreted in 24 hours. The main enzymes are trypsin, amylase, and lipase. Deficiency of the external pancreatic secretion produces a typical *pancreatic triad.* This consists of:

1. Steatorrhea (bulky, gray, frothy stools).
2. Creatorrhea (excess of protein and undigested meat fibers in the stool).
3. Diarrhea (due to imperfect digestion and excessive fermentation).

Pancreatic *pain* is aggravated when the patient is on his back but is relieved when he is in a sitting or prone position. This applies to both acute and chronic pancreatic conditions.

Tenderness may be situated anywhere along the involved viscus. For this reason one cannot exactly pin-point pancreatic tenderness but when present it is located supraumblically.

Pancreatic Heterotopia:—Aberrant pancreatic tissue which has no connection with the main mass of pancreatic gland may occur at any site along the gastrointestinal tract. The most common location, however, is around the pyloric end of the stomach and the duodenum. The presence of such tissue has also been recorded in the jejunum and in Meckel's diverticulum. Usually ectopic pancreatic tissues causes no symptoms but those which occur in the region of the stomach or the duodenum may produce pain, hemorrhage, or obstruction and inflammatory changes. When it occurs in the small intestines, particularly in a Meckel's diverticulum, it may act as a spearhead for an intussusception.

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These are usually confused with tumors, polyps, and ulceration. If found during abdominal explorations they should be excised.

Acute Pancreatitis

This condition has been divided into acute edematous and acute hemorrhagic pancreatitis. It is important to diagnose acute pancreatitis *per se* whenever possible since the modern trend toward conservative management lowers both the morbidity and mortality.

The *etiology* may be related to biliary tract disease and the possible presence of a common channel which exists between the terminal bile and pancreatic

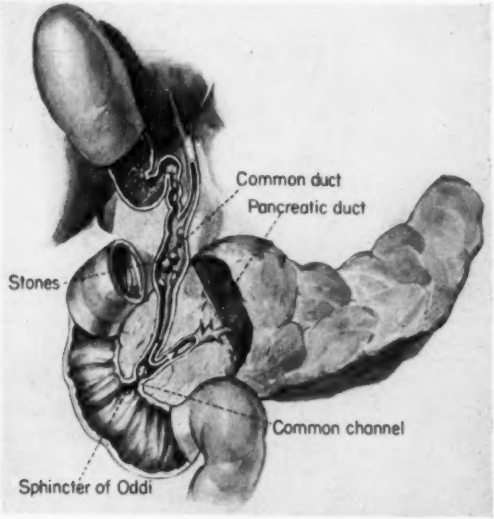

Fig. 1—The Common Channel Theory. This theory presupposes the regurgitation of bile into the pancreas via the pancreatic duct. Two prerequisites are necessary, namely, the existence of a common channel for the pancreatic and common ducts, and a block at the sphincter of Oddi as might be caused by stones, spasms or swelling.

ducts. Fitz in 1889, gave an accurate description of the condition; Opie in 1901, described a case of pancreatitis produced by a stone lodged in the ampulla of Vater, and proposed the "common channel" theory whereby bile regurgitates into the pancreas via the pancreatic duct (Fig. 1). It is presupposed that bile salts activate pancreatic ferments which in turn digest the surrounding tissues. This results in edema, necrosis, and hemorrhage.

Other factors have been associated with the etiology, namely, trauma producing interstitial hemorrhage, bacteria, and ingestion of food and alcohol. I have devised a mnemonic that the causes of pancreatitis may be associated with the letter "B", namely, *B*acteria, *B*lood, *B*ile, *B*ody Juices, and *B*ooze.

Symptoms:—Pancreatitis may affect patients of any age but predominantly those in the middle age group. Symptoms vary depending upon the extent of the disease; with pancreatic edema the symptoms are mild and vague, whereas in pancreatic necrosis they are violent. The *onset* is sudden, and frequently follows the ingestion of a heavy meal and/or alcoholic beverages.

Pain originates in the epigastrium and is constant. It increases to an agonizing severity and is rarely relieved by a single injection of morphine. It tends to radiate through to the back at a level which corresponds with its anterior location; at times it radiates to the left loin. These patients are relieved in a sitting position and are more distressed when lying on their backs. *Nausea and vomiting* appear shortly after the onset of pain. Rarely does vomiting produce relief.

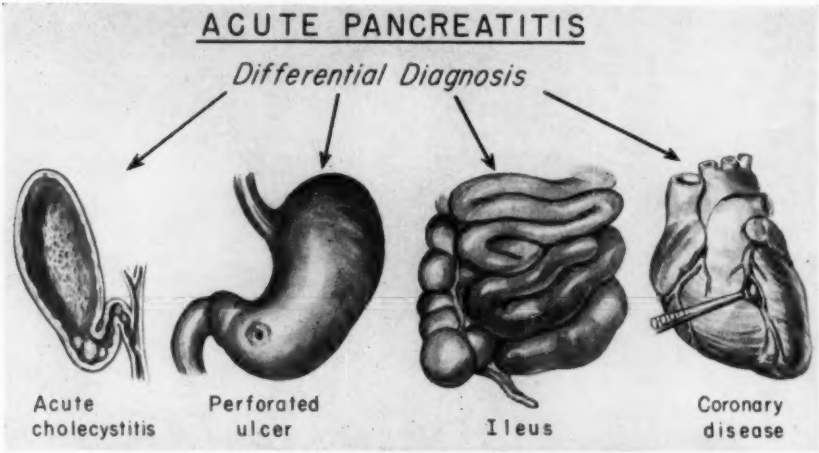

Fig. 2—Among the many conditions which must be considered in the differential diagnosis of acute pancreatitis four must be stressed. They are: acute cholecystitis, perforated peptic ulcer, bowel obstruction and acute coronary disease.

Physical examination reveals an appearance which leaves no doubt as to the severity of the illness. Whereas *shock* is absent in interstitial (edematous) pancreatitis, it occurs in almost every case of the necrotizing type. There is a striking contrast between the severity of the illness and the paucity of physical findings. The *pulse* is weak and at times increased. The *temperature* is normal in early cases. *Tenderness* is almost always present, and is located supraumbilically. As the disease progresses, *abdominal distention* appears, and the *peristaltic sounds become diminished.* Muscle spasm and rigidity are infrequent. *Jaundice* is present in about 25 per cent of the cases and is due to obstruction of the common duct by edema of the head of the pancreas; gallstones at the ampulla, or associated hepatitis may also produce jaundice. Cullen's sign (discoloration

of the periumbilical area) or Grey-Turner's sign (discoloration in the flanks) are supposedly due to extravasation of blood into the retroperitoneal space. These are extremely rare although it is recorded that they are present in 10 per cent of the cases.

Laboratory Data:—Leucocytosis is usually present to a moderate degree, however, this is nonspecific. Hemoconcentration as characterized by a high hematocrit and hemoglobin values occurs early in the course of the disease.

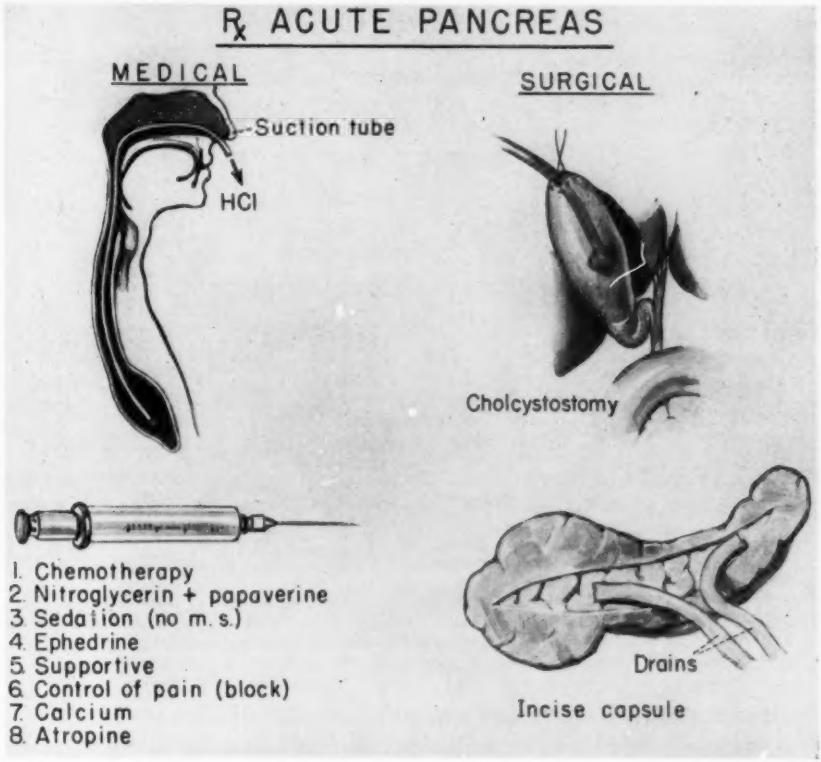

Fig. 3—Treatment of acute pancreatitis. The present tendency is to treat this condition conservatively. Of particular importance is nasogastric siphonage whereby stimulation of secretin is diminished. Some of the methods employed in the treatment of this condition are illustrated in this figure.

The *serum amylase* content is almost always elevated early in the course of the disease. A simple laboratory test devised by Somogyi is based upon the amylolytic action of blood serum on starch. One hundred-eighty Somogyi units are considered an upper limit of normal and any figure over 200 is considered

abnormal. If the disease subsides or if the necrosis is so severe that no more ferments are produced the serum amylase drops abruptly. For these reasons the determination must be made, preferably within the first 48 to 72 hours. Morphine will also give an elevated serum amylase test. It must be remembered, too, that other conditions such as peritonitis, penumonia, and perforated ulcers may also cause an elevated serum amylase test. This test, therefore, is suggestive of pancreatitis but not pathognomonic.

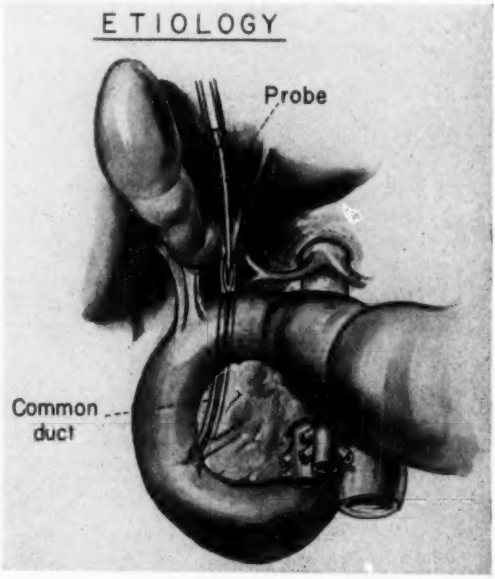

Fig. 4—Trauma to the sphincter of Oddi results in swelling which in turn produces stasis of the pancreatic duct. Such stasis predisposes to acute and chronic inflammation of the pancreas. It is with this thought in mind that I fear forceful dilatation of the sphincter or trauma produced by long limbed T-tubes which pass into the duodenum.

The *serum lipase* test has also been utilized. This remains elevated longer than the amylase value, however, the test requires additional time and equipment.

The roentgenologic findings are not specific. A segmental ileus has been described; it appears as "a sentinel loop" of jejunum.

Differential Diagnosis:—Numerous conditions producing acute abdominal pain could be included herein, however, only the more common ones will be mentioned (Fig. 2).

1. Acute cholecystitis

2. Perforated peptic ulcer
3. Small bowel obstruction
4. Acute appendicitis
5. Mesenteric thrombosis
6. Gallstone ileus
7. Coronary occlusion

Complications:—Acute pancreatitis should be treated conservatively, however, its complications usually require surgical therapy. The complications are cysts, abscess, pancreatic lithiasis, and chronic relapsing pancreatitis.

Prognosis:—Patients with pancreatic edema usually recover but the mortality of acute hemorrhagic pancreatitis still remains high. Delayed surgery or adequate conservative treatment has lowered the mortality in this condition from 50 to 15 per cent (Fig. 3).

Chronic Relapsing Pancreatitis

This condition is a recurrent one, usually progressive, and associated with attacks of upper abdominal pain. It has assumed considerable significance as it is frequently confused with and at times impossible to differentiate from carcinoma of the pancreas, cholecystitis or so-called postcholecystectomy syndrome.

The etiology is undetermined but appears to be associated with acute pancreatitis. The use of large sounds and dilators in the common duct produces trauma to and edema at the ampulla of Vater which in turn results in stasis (Fig. 4). If a common pancreatobiliary channel is present, this trauma can produce stasis and inflammation in the pancreas. The author is of the opinion that long T-tubes which pass through the common duct and into the duodenum may also produce stasis by constant pressure on or obstruction of the pancreatic duct which in turn results in pancreatitis.

Symptoms:—Abdominal *pain*, precipitated by the ingestion of food, is the usual symptom. It is frequently referred to the back and is aggravated by assuming the supine position. Diarrhea is present in about half of the cases. The pain may be severe enough to require sedation. *Jaundice* may be associated with an acute attack or appear as a painless progressive icterus suggesting a malignant neoplasm. The jaundice is a result of edema of the head of the pancreas which compresses the pancreatic portion of the common duct. In about one-third of the cases the symptoms of diabetes are noted first. The physical examination is essentially noncontributory. At times some tenderness is noted supraumbilically.

Laboratory data:—Early in the course of the acute phase the serum amylase may be elevated. Following the administration of secretin, a diminished pan-

creatic excretion can be demonstrated by analysis of the duodenal contents. Glucose tolerance alterations are demonstrable in about one-third of the cases; the presence of excess fat and undigested meat fibers in the stool are also suggestive.

The flat roentgenogram may reveal calcium deposits within the parenchyma of the gland which results either from calcium depositions or pancreatic calculi. No correlation exists between the radiographic demonstration of such calcific deposits and the severity of the clinical picture.

Chronic relapsing pancreatitis is one of the conditions which must be constantly kept in mind and included in the differential diagnosis of peptic ulcer, gallbladder disease, hiatus hernia and coronary occlusion.

Pancreatic Injuries

These have been conveniently divided into:

1. Penetrating
2. Nonpenetrating
3. Operative

Penetrating injuries, although rare in civilian practice, must be considered in any penetrating wound of the upper abdomen. This organ should be investigated in the course of an exploratory laparotomy.

Nonpenetrating injuries are more common. They result from force applied to the upper abdomen, upper lumbar region, or flank. Trivial trauma may also be an inciting factor; these, too, are difficult to recognize clinically.

Operative injuries constitute the most common type of pancreatic trauma. They occur usually during operations upon the biliary tract, the stomach, the duodenum, the spleen, the left kidney, or the adrenal. They are frequently overlooked during the surgical procedure and are detected only in the postoperative period.

The signs and symptoms and laboratory data associated with such injuries have been discussed in the section dealing with the other pancreatic inflammatory conditions.

The complications of pancreatic injuries are pancreatic edema and/or necrosis, hemorrhage, cysts, abscess, internal and external fistulae, and chronic pancreatitis.

CLASSIFICATION OF CIRRHOSIS BASED ON CLINICAL-PATHOLOGICAL CORRELATION

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Cirrhosis of the liver is associated with a variety of clinical manifestations which make diagnosis and especially prognosis of the disease frequently difficult. Different forms of cirrhosis have been recognized. This makes desirable a classification to provide guidance in the understanding of the problems of the individual patient and especially his management. Classification of liver cirrhosis has been a challenge to clinicians and pathologists and several viewpoints have been applied[1-4]. The most obvious is an *etiologic classification*, when the etiology is known. This would lead to a classification such as nutritional (e.g. alcoholic), hepatitic (viral), toxic (chemical), biliary (associated with intra- or extrahepatic biliary obstruction), granulomatous, zooparasitic, hemochromatotic, and cardiac (very rare in contrast to cardiac fibrosis). The etiologic agent, however, is not recognizable in many patients. Moreover, in most forms of cirrhosis the basic features of the disease maintain the disorder even if its original cause, like malnutrition or virus infection, should have disappeared. Therefore, removal of the offending agent, although beneficial as in any other disease, is only part of the clinical management of the disorder. This perpetuation of the cirrhotic process, regardless of the presence of original cause, focuses the interest upon the basic physiopathologic features of cirrhosis.

Cirrhosis can be defined as an altered reconstruction of the lobular pattern and differs thus from simple fibrosis in which just the connective tissue appears increased[2,5]. The basic features responsible for the altered reconstruction are the regenerative nodule[6] in which the arrangement of the liver cell plates has become independent from that of the preexisting lobules and, secondly, connective tissue septa linking portal tracts and central fields and containing anastomoses between branches of portal vein, hepatic artery and hepatic veins[7]. The regenerative nodules are characterized by a tendency to grow, especially on their periphery. This results in the compression of the surrounding structures which includes the blood vessels. The tributaries of the hepatic vein are especially exposed to such pressure effect since they are not surrounded by a firm connective tissue envelope as the vessels in the portal tracts are. The compression of the hepatic vein branches interferes with the drainage of blood from the liver and thus raises the pressure in the portal vein system[8,9]. This factor

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is thus one of the important causes of portal hypertension in cirrhosis, a cardinal feature in this disease. This feature is responsible for the formation of venous collaterals between portal and caval system, especially for the esophageal varices, which may bleed, and also for the splenomegaly causing anemia and leukopenia as hypersplenic manifestations.

The anastomoses between the vascular systems located in the septa are of even greater functional significance. They either result from new formation of vessels (angiogenesis)[10], or from transformation of sinusoids into veins[9]. Communication between hepatic artery and portal vein branches[11,9] represents another cause for the portal hypertension in addition to the compression of the hepatic vein branches and to a questionable influence which fibrosis of the liver may exert upon the portal blood flow[12]. The communications between portal vein branches and hepatic vein tributaries permit a shunt of flow with the blood by-passing the hepatic parenchyma. These portohepatic venous anastomoses have a dual effect. They place the hepatic parenchyma at a circulatory disadvantage and account especially for the centrolobular or centronodular hypoxic necrosis, so frequently seen in cirrhosis, and thus produce liver cell damage not depending upon the original cause of the cirrhosis. Liver cell damage together with portal hypertension produces ascites. These shunts thus maintain the cirrhotic process even if the offender has been removed. The second effect of such a shunt supplemented by the extrahepatic collaterals between portal and caval systems, for instance in the abdominal wall, is the deprival of the organism of the functions of the liver. This is reflected in systemic manifestations of hepatic insufficiency independent of the functional status of the liver itself, for instance manifested in neurologic symptoms (portosystemic encephalopathy)[13].

Portal hypertension, circulatory hepatic insufficiency, reduced service of the liver to the body and ascites thus are the main functional sequelae brought upon by the *regenerative nodules* and *vascular shunts* in any type of cirrhosis independent of its etiology. These two basic pathophysiologic features develop through different pathways. This offers a second grouping of cirrhosis, a *morphogenetic* classification, based originally upon observation of autopsy material and now supplemented by several other aspects.

Three approaches have permitted in recent years a better understanding of the morphogenesis of cirrhosis. The first is the production of hepatic cirrhosis in experimental animals which leads not only to the establishment of etiologic factors, but also to the recognition of initial stages. The second is the three-dimensional study of the cirrhotic liver by means of reconstruction and statistico-geometrical analysis as carried out by Elias[14,15,7]. The third, and probably most fruitful, is liver biopsy which permits follow-up of the development of the process as well as a correlation between the clinical and laboratory manifestations and the pathologic picture. With these added approaches it

appears possible to apply the morphogenetic classification to the various stages the clinician sees in his patients.

Three main pathways lead to the transformation of the normal into cirrhotic parenchyma[7] (Fig. 1). The first pathway is initiated by *necrosis* of circumscribed portions of the parenchyma, either massive or submassive, or by coalescence of areas of focal necrosis. In the massive necrotic area the connective tissue framework collapses and portal tracts and central fields become closely approximated. A postnecrotic scar develops which, as such, does not necessarily indicate a cirrhosis. Near the collapse, fissures develop in the persisting parenchyma into which subsequently connective tissue membranes are laid down and thus septa are formed in the intact parenchyma which distort its architecture. In other areas the necrosis of the parenchyma is submassive rather than massive. Isolated parts of the parenchyma, varying in size from fragments of a lobule

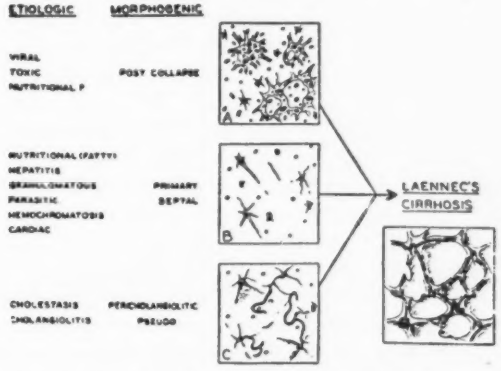

Fig. 1—Schematic presentation of etiologic and morphogenetic factors, as well as of the pathways, for the development of cirrhosis (from Popper, H., and Elias, H., Am. J. Path., **31**:420, 1955).

to continuous portions of several lobules, survive. The parenchymal remnants become nodules, varying markedly in size and shape. They show great regeneratory tendencies in view of the preceding destruction of vast areas of the liver. The collapsed areas become connective tissue septa, which are sometimes very thick; some sinusoids in them develop into veins forming the vascular shunts. In the nodules consisting of several lobules, the lobular architecture is preserved and intact portal tracts and central veins are seen. This postnecrotic cirrhosis or postcollapse cirrhosis may involve predominantly one area of the liver (lobular form) or may produce large readily palpable nodules throughout the organ. Sometimes it is fine granular and then differs little from end stages of other types of cirrhosis[16]. The characteristic features are unequal involvement throughout the organ and the preceding episode of extensive necrosis (for instance of the character of acute yellow atrophy) which is usually reflected in an episode

of severe jaundice[17]. The lesion follows very severe viral hepatitis or toxic necrosis. Postnecrotic scars, however, are also seen in nutritional fatty liver in alcoholics in this country and in persons suffering from malignant malnutrition in the tropics. Sometimes no definite cause can be elicited in the history of the patient[18]. Postnecrotic cirrhosis may be an incidental finding at autopsy, but if it is accompanied by hepatic insufficiency and jaundice, the prognosis is grave and the manifestations of hepatic failure usually exceed those of portal hypertension[18].

A second pathway to cirrhosis is the diffuse development of connective tissue *septa* and the diffuse formation of regenerative nodules, in part from parenchymal cell groups separated by the septa or entrapped in them. A typical example of this diffuse septal cirrhosis, often called portal cirrhosis (though the lesion does not necessarily start in the portal tracts), is the fatty cirrhosis following various types of prolonged fatty metamorphosis of the liver; in this country it is chiefly the result of alcoholism or, less frequently, of intestinal or pancreatic disease. Usually the patient suffers from imbalance between the dietary factors promoting hepatic fat deposition (lipotropic, e.g. fat, carbohydrates, or high caloric food in general) and those preventing it (lipogenic, e.g. choline, methionine, protein, or starvation[19]). Not necessarily, however, does every type of severe fatty metamorphosis lead to fibrosis and cirrhosis. Some consider fat deposition alone the cause of the cirrhosis formation[20,21], while others[22,23] assume the necessity of additional factors, such as necrosis. The mechanism by which fatty liver proceeds to cirrhosis is therefore not fully established, but much evidence points to the importance of acute infections of various types to which the patient with fatty liver is more susceptible, and to the toxic effects of which the liver itself seems to respond with necrosis[24]. The acute phase of this lesion is the large fatty liver with jaundice and sudden hepatic failure, frequently fatal. In the subacute phase, which was called florid cirrhosis[25], diffuse liver cell damage is accompanied by diffuse formation of collagenous membranes and patchy regeneration. Both of these stages are frequently associated with infections and with clinical and laboratory evidence of hepatic failure, rapidly developing ascites, jaundice and, especially in the florid cirrhosis, *spider nevi*. The septum formation starts around fatty cysts[20], around areas of necrosis and on the borders of regeneration and degeneration. As the septum formation progresses the lobular architecture becomes distorted, regenerative nodules predominate and a fatty cirrhosis develops. Eventually the fat disappears either because of starvation or possibly due to therapy. The liver shrinks, becomes small, fine granular, and resembles the end stage of other forms of cirrhosis. Not only fatty metamorphosis may initiate this diffuse nodule and septum formation from which no part of the liver is spared, but a similar process of septum formation may follow granulomatous diseases (e.g. sarcoidosis or tuberculosis), hemochromatosis, infestation by parasites or prolonged severe right heart failure (as in tricuspid incompetence or con-

strictive pericarditis) and probably also viral hepatitis. This diffuse septal cirrhosis is characterized by gradual insidious onset occasionally with transient episodes of hepatic failure and jaundice, but eventually leading to death by the sequelae of portal hypertension slightly more frequently than those of hepatic insufficiency.

The third pathway to cirrhosis is ushered in by lesions in the intra- and extrahepatic bile ducts, mainly obstruction and inflammation. This results in inflammatory exudate around the small bile ductules, the cholangioles, and extension of this exudate along proliferating cholangioles in a streak-like fashion throughout the lobule. This is followed by a diffuse *periductular fibrosis*. In this stage, the lobular architecture of the enlarged liver is obscured but not destroyed and the term cirrhosis does not really apply. Late in the disease, however, septa and regenerative nodules form and then the morphological, laboratory and clinical manifestations of a diffuse cirrhosis of septal type develop. This biliary or pericholangiolitic cirrhosis is rarely caused by extrahepatic obstruction without infection. Adults do not survive complete obstruction long enough to develop cirrhosis, but children with congenital biliary atresias do. It may result from an intrahepatic disturbance of the bile flow in the form of cholangiolitis and is then called primary biliary cirrhosis (Hanot)[26,27]. It is also caused by extrahepatic biliary obstruction associated with bacterial infection, so-called secondary biliary or cholangitic cirrhosis, frequently after strictures[28]. Jaundice is usually in the foreground, liver cell damage is not very prominent and ascites a late manifestation. Patients with the primary form survive for a long time, whereas those with the secondary type succumb to the sequelae of the bacterial infection, such as liver abscesses.

All three morphogenetic pathways to cirrhosis converge to a terminal stage of a nodular liver in which the route of development can often not be recognized any more and for which the name *Laennec cirrhosis* best applies. The pathways do not necessarily reflect a given etiology. Hepatitis initiates the postnecrotic pathway but may possibly also produce a diffuse septal cirrhosis. Most nutritional cirrhoses in alcoholics are diffuse septal, but not infrequently broad postnecrotic scars are seen in addition, indicating in the same liver the remnants of several pathways.

The morphogenetic classification assists in the understanding of the development of the cirrhotic process and in its diagnosis. It does not, however, take into account the stages of the disease and specifically does not provide for evaluation of the clinical and functional picture in an individual patient. For this purpose a third classification, namely a *functional-therapeutic*, has been proposed similar to the one so useful in cardiac diseases[29]. For such a functional classification, three aspects of cirrhosis appear of main importance. One is the degree of damage of the parenchymal hepatic cells produced by either the original cause or the cirrhotic process itself. This damage is reflected in the degree of jaundice, the incidence of hemorrhage, especially gastrointestinal, and

in *spider nevi* and, to some degree, in ascites as well as in abnormal results of most of the hepatic tests and, of course, also in morphologic manifestations apparent in liver biopsy. The second aspect to be considered is the degree of the cirrhotic process which may be minimal to far advanced. Little correlation exists between the extent of cirrhosis formation and the laboratory findings or with the clinical manifestations with the exception of splenomegaly and possibly shrinkage and nodularity of the liver. Extent of cirrhosis formation is thus best recognized in liver biopsy. The third and probably most important aspect is the rate of progression of cirrhosis, whether the lesion is arrested, advancing or florid, that means rapidly progressing. Progression is reflected in jaundice, ascites, splenomegaly, *spider nevi* or palmar erythema, which are far more commonly encountered than in arrested cirrhosis. Also the serum level of gamma globulin is more often elevated. The described features may occur in all combinations, for instance, far advanced cirrhosis may be present without liver cell damage and without any signs of progression and thus be an incidental finding (latent cirrhosis).

In summary then, if one attempts to classify cirrhosis from a coordinated clinical-pathologic viewpoint one can combine an etiologic connotation, where possible, with a morphogenetic description and finally designate the functional involvement reflected in the degree of liver cell damage, the extent of the cirrhotic process and its progression.

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THE USEFULNESS OF CORTICOTROPIN AND CORTICOIDS IN PATIENTS WITH LIVER DISEASE*

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"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us. . . ."

These opening lines of Dicken's *Tale of Two Cities* describe colorfully our present state of knowledge about hepatic diseases and their treatment. Confusions and contradictions reign supreme; old "well established facts" are enthusiastically discarded. New and untested ideas are enthusiastically espoused. In the late 1930's and early 1940's the importance of high protein diets in the treatment of liver disease was firmly established on the basis of clinical and experimental data[18]. These ideas are being challenged because of the apparent worsening of certain patients with portal cirrhosis when exposed to a high protein diet[12,15]. The deleterious effects of high fat diets in portal cirrhosis and in animals exposed to toxins was demonstrated clinically and experimentally[18]. This is likewise brought into question by at least one observation[13]. The importance of absolute bed rest in the treatment of infectious hepatitis seemed to be established by convincing evidence during World War II[1]. This concept is also being modified by more recent observations[3,4].

I am pointing out these changes and contradictions not because I espouse wholeheartedly the "1955 style" of hepatology (the contrary is actually the truth) but they highlight the flux, contradictions, and confusion in hepatology today.

By the subsequent remarks I may inadvertently add to this confusion, but I shall attempt to crystallize a few untarnished ideas. Corticotropin and the corticoids being relatively new therapeutic agents, it was to be expected that they would be given a trial in resistant and hopeless cases of liver disease. From a survey of the physiologic and pharmacologic activity of these potent substances one may readily conclude that they have deleterious effects on the liver[18].

Deleterious Effects of Steroids

It has been noted that in adrenalectomized animals there is increased protein synthesis and decreased protein break down. When adequate exogenous protein intake is assured, the adrenalectomized animal shows increased rate of

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hepatic regeneration after partial hepatectomy[4]. Cortisone can produce fatty livers in animals and man. Levin and Farber have demonstrated that neither fatty livers nor ketosis can be produced in adrenalectomized animals. Both adrenalin and cortisone are necessary to produce ethionine fatty livers[20].

In addition to the production of fatty livers by cortisone, the steroids increase protein catabolism which would enhance the protein disturbance in patients with liver disease. The effect of these hormones on sodium and potassium would act to aggravate the sodium retention and potassium loss already existing in hepatic dysfunction.

Favorable Effects of Steroids

Some salutary effects of steroids on liver disease may be culled from the literature. Thus the rapid fall of liver glycogen noted by Long and coworkers[11] in adrenalectomized animals suggests that the adrenal hormones may aid in maintaining adequate liver glycogen which may be important for normal liver function. This diminution of liver glycogen in the adrenalectomized animals may, however, depend upon the inability of the liver to deaminize amino acids and convert them into glucose[10]. Furthermore, Berman[2] has noted that adrenalectomy inhibits regeneration after partial hepatectomy and adrenocortical extracts hastened the process in these animals. The observation by Schwartz[17] that cortisone inhibits dietary hepatic necrosis in the rat is significant.

Clinical Observations

Although most of the experimental observations suggest that these hormones are more likely to be harmful than useful, the source of the bulk of the information (animal experiments) and artificial settings does not make it completely applicable in clinical medicine. These hormones have been found to be potent therapeutic agents in combatting certain types and certain phases of liver disease.

Acute Hepatitis

In the early observations beginning about 1950 improvement in certain cases of acute viral hepatitis has been noted with the use of ACTH and cortisone[18]. Two actions of these hormones make them particularly useful in acute viral hepatitis. These are: 1. stimulation of appetite and 2. reduction of serum bilirubin.

In spite of these desirable effects the hormones are not indicated in all cases of viral hepatitis. According to recent observations by Evans and coworkers[6] the routine use of these hormones in viral hepatitis results in a higher rate of relapses. It's likely that the hormones interfere with antibody formation. It should be a general principle not to use potent and potentially harmful drugs in a disease which has such a high rate of spontaneous recovery as viral hepatitis.

Even the appetite stimulating effect may not be entirely an unmitigated blessing since it has been suggested that the appetite stimulating effect of the steroid may be an attempt to counteract their protein breakdown effect.

These hormones should be reserved for patients with acute hepatitis who show a prolonged course with persistent anorexia and persistent unremitting jaundice or who show signs of going into hepatic failure. Hepatic coma will be discussed under a separate heading. The type of case in whom these hormones are useful is represented by the following patient:

A male patient 27 years of age developed infectious hepatitis. Early in the disease he developed marked anorexia with a marked aversion to food. Even the sight and smell of food nauseated him. Vomiting was frequent. Although the

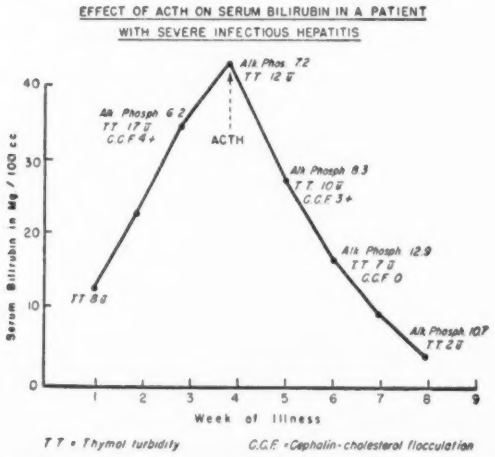

Fig. 1—From: Spellberg, M. A.: Diseases of the Liver. Grune & Stratton, N. Y., 1954.

patient was placed on a high protein diet, his caloric consumption was very low and he had to be given intravenous glucose with ascorbic acid and the B-complex vitamins. The liver was enlarged about 8 cm. below the costal margin and was markedly tender to palpation and percussions. The spleen was palpable. The icterus increased and the serum bilirubin was 40 mg. per cent at the end of 4 weeks (Fig. 1). The serum albumin was decreased to 2.7 gm. and the globulin was 4.0 gm. per cent. At that point the patient was given 20 units of ACTH daily, intravenously. There was nearly a 50 per cent drop of the serum bilirubin within one week (Fig. 1). This dose was continued for two weeks and gradually discontinued. There was prompt return of appetite and the caloric intake became adequate. The icterus disappeared in about 4 weeks and the patient made an uneventful recovery. He showed no evidence of relapse or chronicity on follow-up.

Chronic Hepatitis and Posthepatitic Cirrhosis

In chronic hepatitis, that is hepatitis continuing beyond 6 months, and in posthepatitic cirrhosis the steroids seem to be of distinct value. This is especially true if the patient is jaundiced. Therefore the posthepatitic cirrhosis in which these hormones are useful would fall into the classification of biliary or cholangiolitic cirrhosis.

The following case demonstrates the usefulness of these agents in a patient with posthepatitic, cholangiolitic cirrhosis.

N. D., a boy age 17, developed malaise, anorexia and a low grade fever in January, 1953. This was regarded as an upper respiratory disease and after subsidence of fever he was allowed to return to school. In February symptoms recurred and icterus was noted. Because of persistent icterus the patient was hospitalized. A history of jaundice at age of 9 was elicited. *Spider nevi* were

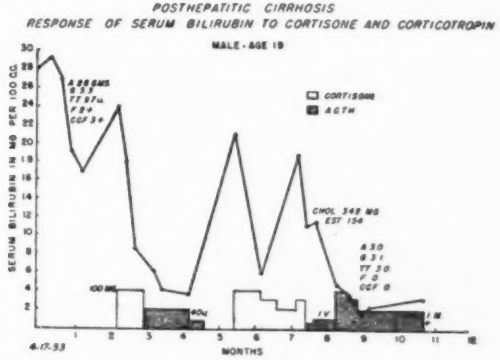

Fig. 2

noted on his left upper arm. The liver was enlarged to 6 cm. below the right costal margin. The spleen was palpable. The serum bilirubin was 28.0 mg. per cent. On absolute bed rest and intravenous glucose and vitamins the patient improved slightly. His serum bilirubin decreased to 16.8 mg. per cent and the patient was discharged to his home.

He did not do well at home, his jaundice increased and anorexia continued. He was rehospitalized and on June 29 the serum bilirubin had again increased to 24 mg. per cent (Fig. 2). At that time he was placed on 50 mg. of cortisone intramuscularly twice daily. The serum bilirubin dropped to 8.4 mg. per cent in 2 weeks. It should be noted that the cholesterol and esters rose from 96 mg. and 0 per cent respectively to 197 mg. and 61 per cent esters and the flocculation tests became normal. There was marked improvement of appetite and weight gain. After 3 weeks 40 units of ACTH gel intramuscularly was substituted for the cortisone. He was discharged to his home on 40 units of ACTH gel and the

serum bilirubin decreased to 3.6 mg. per cent. The ACTH was gradually reduced and then discontinued (Fig. 2).

Upon discontinuance of steroids, the serum bilirubin again rose to 21.0 mg. per cent. On 100 mg. of cortisone daily the serum bilirubin dropped to 6.2 mg. per cent in 3 weeks but rose again when cortisone was decreased.

The patient was rehospitalized and on 20 units of ACTH intravenously a prompt drop of the serum bilirubin to 4.4 mg per cent was obtained. This was replaced by ACTH gel 80 units intramuscularly daily, and the serum bilirubin decreased to 1.5 mg. per cent. The patient's sodium intake was restricted and supplementary potassium was given. Carboresins were administered to minimize further the sodium retention. The patient was discharged to his home on oral cortisone 100 mg. daily in divided doses and maintained on cortisone, which was gradually decreased, in about 3 months.

The patient has remained anicteric for about 18 months. The flocculation tests are normal, the urine contains no bilirubin but urobilinogen in higher than 1:20 concentration and the BSP retention remains over 30 per cent. His liver is barely palpable but not tender. His appetite is good; there is no undue fatiguability and the patient has returned to school.

Needle liver biopsy at the height of the jaundice in 1953 showed marked bile stasis, marked bile duct hyperplasia, and marked round cell infiltration as well as severe scarring. This is a histologic picture of a posthepatitic biliary cirrhosis (Fig. 3). Another biopsy done in 1954 revealed a reduction in bile stasis and some reduction in the exudative process. Bile ducts were numerous and there was a good deal of scarring. It should be emphasized that no fatty infiltration occurred in spite of the prolonged steroid therapy (Fig. 4).

Comment

This patient demonstrates admirably the marked and consistent effect of steroids on the hyperbilirubinemia of posthepatitic cirrhosis. We could practically turn the jaundice off and on by increasing and decreasing the steroids. The steroid had to be continued for about 18 months at which point the liver was apparently able to take over this function without assistance. The patient's general condition improved, his appetite continued satisfactory after discontinuance of steroids. The liver tenderness disappeared and did not recur. I feel that the hormones helped this patient over a critical period. In addition to the clinical improvement and reduction of serum bilirubin there was also improvement in other liver function tests. The cholesterol at first was low and the esters were absent. Later the cholesterol reached an excessively high level of 342 mg. per cent. This later decreased to 177 mg. per cent. The albumin and globulin likewise returned to a normal level. The only residual evidence of disease is the urobilinogenuria and BSP retention.

In spite of the prolonged use of the corticoids no serious side-effects were encountered. Moon face, striae, and acne developed, slight edema developed but massive sodium and water retention was prevented by curtailing sodium intake, administration of carboresins and potassium chloride.

Hepatic Coma

Death from liver failure is usually preceded by a set of symptoms referable to the central nervous system, culminating in coma. Recovery from hepatic coma has been extremely rare. The use of ACTH and corticoids has improved somewhat the prognosis of hepatic coma although it remains a most threatening phase in the course of liver disease. Ducci and Katz[5] noted favorable effects from the use of cortisone in two patients with fulminant hepatitis in hepatic coma. Sborov and coworkers[16] however, failed to rescue two patients from hepatic coma, and Evans and coworkers[6] experienced failure in six.

I have used these hormones in 6 patients in hepatic coma. The type of liver disease included 3 patients with posthepatitic cirrhosis, and one each with chronic, subacute and acute hepatitis. Only one of these 6 patients survived and is still alive 8 months after her first episode of coma.

This patient, G.S., is a 25-year old female who acquired infectious hepatitis about 6 years previously. She entered the hospital in the 5th month of pregnancy, jaundiced, with *fetor hepaticus* and hepatosplenomegaly. She delivered a 7 months premature but viable infant and 3 days later went into hepatic coma. She was receiving 20 units of ACTH intravenously antepartum, this was increased to 100 units intravenously daily. Within 24 hours she responded and after 72 hours was out of coma. The ACTH was changed to the intramuscular route and decreased to 40 units intramuscularly. About 2 weeks later the patient again went into hepatic coma. Administration of 100 units ACTH intravenously daily again resulted in a clearing of the sensorium and return to the precoma state within 48 hours. A reduction of the ACTH to 60 units by the intramuscular route resulted in mental confusion. This responded to an increase of ACTH to 100 units daily, intramuscularly. Except for a transient period of euphoria the patient remained alert while the ACTH was decreased very gradually. The patient was discharged 4 weeks after the last episode of coma on 40 units of ACTH intramuscularly.

This patient demonstrates dramatically the effect of corticotropin on central nervous system function in certain cases of hepatic coma. The postpartum hepatic coma may have been due to a spontaneous reduction of endogenous adrenal steroids at the termination of pregnancy and it was necessary to stimulate her adrenal gland more vigorously with large amounts of ACTH. Reduction of ACTH later resulted in a recurrence of coma, which again responded to increased ACTH.

Another interesting feature of this case is that increased protein intake did not result in nervous or psychic abnormalities. After the second episode of coma

the patient's protein intake was limited to 60 gm. per 24 hours. The patient was confused one day; the ACTH was increased and the patient became euphoric. After 1 week the protein intake was increased to 120 gm. per 24 hours. The patient's appetite was good and she ingested all of the protein supplied but showed no untoward effect. This indicated that the apparent deleterious effects of proteins on the psychic symptoms of grave liver disease does not occur in all types of cirrhosis.

Corticoids in Portal Cirrohsis

These hormones are probably not as useful in classical portal cirrhosis as they are in the entities discussed above. Favorable reports have appeared in the literature about the use of these hormones in portal cirrhosis[21].

Hepatic coma occurring in portal cirrhosis can be usefully treated with steroids. Good results can be especially expected in the stage of precoma. The steroids may also be useful in prolonged icterus and severe anorexia of portal cirrhosis. One should be watchful for sodium and water retention when these hormones are used in portal cirrhosis.

Corticoids in Biliary Cirrhosis

Hepatic (primary) biliary cirrhosis is frequently the end result of an intrahepatic inflammatory process which compromises the intrahepatic bile ducts[18]. The primary process in many patients with biliary cirrhosis may be viral hepatitis. Steroids should have a favorable effect on the reduction of the intrahepatic inflammatory process and a favorable effect on the hyperbilirubinemia. The steroids should therefore be given a trial in all cases of biliary cirrhosis. In spite of the theoretical indication these drugs are not always successful.

Perhaps the difference in response of various types of biliary cirrhosis to the steroids may depend on the stage in which they are used as well as on the etiologic factors which produced the cirrhosis. Thus N. D., whose hyperbilirubinemia responded remarkably to steroids, is in marked contrast to G. S., the pregnant woman whose bilirubin continued going up in spite of the steroids. It is suggested that when there is a marked inflammatory reaction in the liver as evidenced by an abundance of round cell infiltration the response to the steroids is more marked than when the active inflammatory process is minimal.

Corticoids in Jaundice of Doubtful Etiology

One occasionally encounters a patient whose jaundice cannot be positively classified in spite of all the clinical and laboratory data. In such instances laparotomy with exploration of the extrahepatic ducts has been resorted to. In some of the cases I have seen, even though no extrahepatic obstruction was found or removed a drop in the serum bilirubin has occurred[19]. The possibility suggests itself that the drop in serum bilirubin may have been the result of a stimulation of the adrenals by the stress of surgery.

Because of these considerations, since 1952, I have attempted to use these hormones as a therapeutic test in borderline cases. While its drawbacks as a test in the differential diagnosis of jaundice will become apparent in the subsequent discussion, it still has a definite use in some cases with obscure types of jaundice.

It is true that purely mechanical obstruction such as would be produced by a calculus or tumor should not be influenced by hormone administration. In addition to the mechanical obstruction by these agents, however, an inflammatory reaction plays a role in the completeness of the obstruction. Thus a calculus obstructs the common duct not only by its presence in the duct but also because it sets up an inflammatory edema. Thus if the steroids help to reduce the edema the jaundice may subside while the stone remains in the common duct. I have seen the icterus in a patient with cholecystitis and chole-

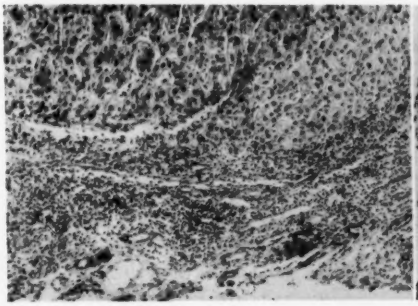

Fig. 3

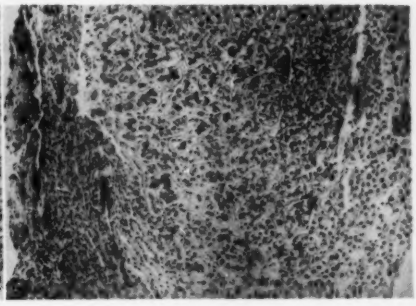

Fig. 4

Fig. 3—Liver biopsy of N. D. in 1953 (x200) showing marked lymphacytic infiltration, bile duct multiplication and fibrosis.

Fig. 4—Liver biopsy of N. D. in 1954 (x200) after about 6 months of steroid therapy. Note the absence of fatty infiltration and decrease of round cell infiltration, but fibrosis is well developed, left side of illustration.

lithiasis and cystic duct stone respond to steriods. This response may have been the result of inhibition of the inflammatory reaction set up by the calculus.

The jaundice due to carcinoma of the pancreas has always been considered to be unremitting. The following case illustrates that even in carcinoma of the pancreas the jaundice may be due to an associated pancreatitis which responds to the anti-inflammatory influence of the steroids.

S. L. was a 48-year old physician who had a cholecystectomy and common duct exploration and drainage about 1 year before the jaundice recurred. It was not clear whether the recurrent jaundice was due to an obstruction of the duct by cicatrix, tumor, or inflammation. The prompt drop of the serum bilirubin upon administration of 100 mg. of cortisone intramuscularly suggested that the jaundice was due to a cholangitis. The alkaline phosphatase, remained

elevated and even increased (Table I). The patient was subsequently operated on again and a carcinoma of the pancreas was found.

Another illustrative case is that of F. M., a 57-year old female who had a cholecystectomy for cholelithiasis 6 years ago. She developed epigastric pains radiating substernally for which she had an epigastric hernia repaired in January, 1955. She had recurrence of pain which radiated substernally, developed nausea, vomiting, pruritus and jaundice. She had an exploratory laparotomy at the hospital where she had the previous surgery and no common duct obstruction was found, although the common duct was not opened. Liver biopsy was done and showed an intrahepatic cholangitis.

TABLE I

CORTISONE IN POSTHEPATIC JAUNDICE
Ca Pancreas Male Age 48

		Ser. Bil.	Alk. Phosp.
7-29-53		12.2	13.4
	Cortisone		
8-3-53		10.4	12.1
8-12-53		6.0	24.3
8-15-53		4.0	32.5
8-24-53		3.3	32.2
8-29-53		1.9	21.2
9-11-53		1.2	43.0

When we saw the patient we were impressed with the pain which suggested, to us, as well as to the patient, a biliary colic. The liver function tests likewise confirmed the opinion that this was a posthepatic jaundice. We were hesitant in subjecting the patient to another exploratory laparotomy with its increased technical difficulty and the possibility of injuring the common duct. We placed her on 60 units of ACTH gel and the jaundice which was present for 10 weeks rapidly and completely disappeared (Fig. 5).

Although I am not convinced that the beautiful response in this case indicates that the jaundice was hepatic in origin, the disappearance of the jaundice and the patient's return to normal health under steroid therapy eliminated the need for further surgery. The possibility exists that the patient has a common duct stone which has been present for 6 years without compromising the flow of bile. The intraabdominal disturbance of the surgery resulted in associated edema of the duct with obstruction. The steroids reduced the edema, and along with it the jaundice.

Mode of Action

The rapid amelioration of icterus in patients with liver disease when exposed to steroids brings up the question of how the hormones accomplish this. It's well established that in various types of diffuse liver disease there is increased hemolysis[18]. Since the steroids are known to reduce hemolysis it's been postulated that the reduced hemolysis reduces the elaboration of bilirubin, and thereby the icterus is reduced. I have not been convinced that with patients who show a good response to the steroids there is evidence of unusual hemolysis. These patients did not have anemia, reticulocytosis or unusually large amounts of urobilin in the urine.

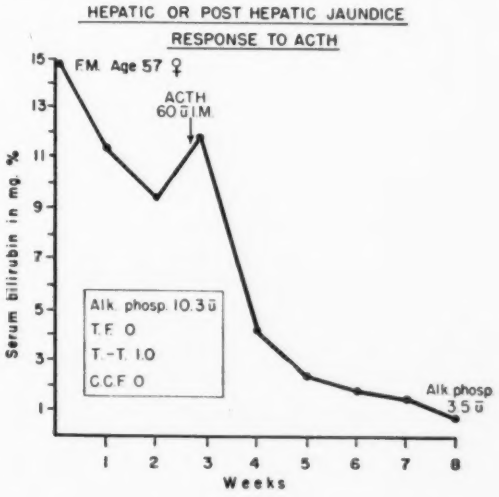

Fig. 5

It has also been suggested that the steroid hormones produce increased bilirubin excretion either by increasing the volume of bile or by increasing the concentration of bilirubin in the bile. I am inclined to the view that the steroids act by virtue of their anti-inflammatory action. The reduction of the exudation around the cholangioles or in the large ducts results in improved drainage of bile and disappearance of hyperbilirubinemia.

Dosage, Type of Drug, and Mode of Administration

In the treatment of severe hepatitis, chronic hepatitis, or cirrhosis the dosage of steroids is small or moderate. ACTH is preferred and if used intravenously only 20 or 40 units over an 8-hour period are sufficient. Intramuscular ACTH can be given as the gel in one dose or in solution in divided doses 40 to 100 units per day. Cortisone can be given orally 100 mg. in divided doses in 24

hours. Hydrocortisone 40 to 60 mg. orally may be utilized. We have done blood determinations of plasma hydroxysteroids after oral administration of hydrocortisone in a jaundiced individual and found that the hormone is well absorbed even when there's a deficiency of bile in the gastrointestinal tract.

The dosage in hepatic coma is much higher. ACTH is given intravenously, 100 units daily. Hydrocortisone intravenously is given in a dosage of 100 mg. or more daily. Although cortisone has been given in as much as 500 to 1,000 mg. daily, such large doses of hydrocortisone do not seem to be indicated.

The duration of therapy varies from a few days in hepatic coma to many months in posthepatitic cirrhosis. The steroids are gradually reduced; if a recrudescence of symptoms or signs occur the dosage has to be correspondingly increased. This was demonstrated in our patient with posthepatitic cirrhosis.

Complications of Steroid Therapy

The complications of steroid therapy to be watched for are the same as those that may occur when these hormones are used in the therapy of other diseases. These include sodium and water retention and all the events which follow in their train. Since there is a tendency for water and sodium retention in liver disease anyway, such conditions as edema, ascites, and pulmonary edema may become dangerous. Hypervolemia may induce rupture of esophageal varices.

These complications are to be forestalled by watching the urinary output, decreasing the sodium in the diet and the administration of carboresins. Hypopotassemia is to be prevented by administration of potassium salts.

There is an abundance of evidence that the steroid hormones increase pepsin secretion and provoke peptic ulcerations of the stomach and duodenum. Therefore upper gastrointestinal ulceration and hemorrhage must be watched for, and treated promptly and vigorously when it occurs. I have seen diffuse ulcerative gastritis with hemorrhage in some patients who died in hepatic failure in spite of corticoid therapy. Since death from hepatic failure may be accompanied by such bleeding it's uncertain whether the steroid therapy is responsible for this complication.

Psychosis from steroid therapy in liver disease has never been observed by me, nor has it been reported in the literature. The development of a fatty liver is a theoretical possibility which has not developed in my patient who received this drug for many months.

Summary

ACTH and the corticoids are useful therapeutic agents in the following types of liver disease: 1. protracted hepatitis with jaundice 2. fulminating hepatitis 3. hepatic coma 4. posthepatic cholangiolitic cirrhosis, and 5. perhaps other types of biliary cirrhosis. It may be of limited value in certain phases of

portal cirrhosis. It may have some limited value as a therapeutic test in differentiating between "medical" and "surgical" jaundice, the cause for errors are pointed out.

In one patient with posthepatitic cirrhosis the hormones were used for 18 months with abolition of jaundice. The serum bilirubin could practically be titrated with the steroids. No fatty liver developed in this patient.

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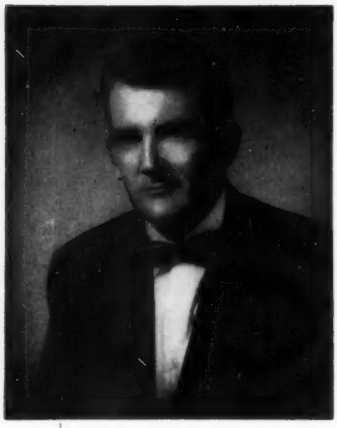

President's Message

As my term of office is drawing to a close, I shall attempt to survey our activities and progress during the past year. Most encouraging for the future is the teamwork we have all shown in the past. As our older men with young ideas are replaced by our younger energetic confrères, sectionalism in the College will recede into the limbo of half-forgotten things.

With the assistance of our executive director, Mr. Daniel Weiss, administration has been simple. By channeling all information through the headquarters office and by giving *carte-blanche* to our committee chairmen, your officers and Board of Trustees have acted purely in an advisory capacity. Furthermore, our Secretary-general, Dr. Lynn Ferguson has inaugurated a six months' progress report on our membership, showing specialties and sectional representation.

In the way of expansion, the New Orleans regional meeting and the Levin Lectureship have done much to strengthen us in the deep South. I sincerely believe that the restoration of chapters in the near future will be an added stimulus to our regional organizations.

I would suggest that in the future attendance at a certain percentage of postgraduate courses be made obligatory for Fellows, Associate Fellows, and Members. This would make us the first organization in any specialty field to make continued education a requirement for maintaining affiliation.

I hope to have the pleasure of seeing you at our Annual Convention in New York City in October.

I. J. Nix

EDITORIAL

Jaundice

Hepatitis and diffuse liver damage from toxins or poisons show varying degrees of partial obstructive jaundice syndrome, including dye retention. The cases with the severest liver damage will show a positive galactose tolerance test and possible hypoglycemia, and at times, disturbances in the coagulation of the blood. In the urine there is an increase in the amino acids with a relative increase of the total nitrogen in the form of ammonia, and rarely leucin and tyrosine crystals are observed.

Catarrhal jaundice or acute hepatitis is the commonest condition in this group. Weil's disease, and yellow fever are rare febrile diseases with a similar picture. In any of this group the complete obstructive jaundice syndrome may develop. Syphilis and postarsphenamine hepatitis are (other organic arsenicals may also produce it) rare since introduction of the antibiotics. Dye retention is more marked in proportion to the icterus index than in other types of jaundice. Less common causes of a similar syndrome are cinchophen, chloroform, phosphorus, carbontetrachloride and phenlyhydrazine poisoning. Recently we have encountered many jaundiced patients who have been sensitive to thorazine.

Acute yellow atrophy or icterus gravis:—This is probably simply a hyperacute destructive hepatitis which may result from any of the conditions here listed. It is very rare but relatively more common in pregnant women than in other individuals. The most extreme impairment of liver function occurs in this condition.

Complete obstructive jaundice:—This is characterized by clinical jaundice, clay colored stools in which the tests for urobilinogen and bile pigment are negative, dark urine containing bilirubin but no urobilinogen, and absence of bilirubin from fluid aspirated from the duodenum. The icterus index is usually over 50 and may be as high as 200. This is present whenever bile is prevented from entering the intestinal tract no matter what the cause of the obstruction. The obstruction may be due to carcinoma of the head of the pancreas, the biliary tract or the adjacent lymph nodes, to stone, to scar tissue contraction, to enlargement of the nodes, to lymphadenitis, metastasis, Hodgkin's disease, lymphosarcoma, leukemia, or to a sufficient degree of hepatitis or liver edema to obstruct the flow of bile within the liver. It may also occur from tumors of the liver so located as to obstruct both hepatic bile ducts. In all cases, dye excretion is impaired and if diffuse liver damage is absent, the galactose tolerance test is normal.

Partial obstructive jaundice:—This is characterized by an icterus index of 6 to 150 and at times bilirubin may be present in the urine. It differs from complete obstruction by finding urobilinogen in the urine and feces, and of bili-

rubin in the duodenal aspirate. Dye excretion varies with the icterus index and there is no indication for this determination. The galactose tolerance test is normal if liver damage is not associated. It differs from hematogenous jaundice in that bilirubin may appear in the urine and a direct van den Bergh test may be obtained on the blood serum.

Hepatocellular jaundice:—This is a syndrome of partial or, less commonly, complete obstructive jaundice plus the presence of impaired liver function as determined by the galactose tolerance test. It occurs in diffuse liver disease such as cirrhosis, catarrhal jaundice, Weil's disease, phosphorus or chloroform poisoning.

Hematogenous jaundice:—An icterus index above 6 with a negative direct van den Bergh characterizes this type of jaundice. There is urobilinogen in the urine with a negative test result for bilirubin in the urine. Bilirubin is present in the duodenal fluids and the feces are usually darker in color than normal and if quantitative tests are done, will show an increased excretion of urobilinogen. It is differentiated from complete obstructive jaundice by the dark stools and positive tests for urobilinogen in the urine and the absence of bilirubin in the urine. The dark stools, negative direct van den Bergh and absence of bilirubin make it possible to tell it from partial obstructive jaundice. The normal galactose tolerance sets it apart from hepatocellular jaundice. It occurs whenever hemoglobin is destroyed at an excessive rate in the body, therefore, in all forms of internal hemorrhage, intravascular or extravascular hemolysis, hemolytic icterus and malaria; in other words, in all the internal blood destruction groups of anemias and in many instances where internal hemorrhage has not been sufficient to produce anemia. Both hematogenous jaundice and partial or complete obstructive jaundice may be present at the same time, in which case, the laboratory findings will be typical of obstructive rather than hematogenous jaundice. This occurs most frequently in hemolytic icterus which predisposes to formation of bile pigment stones. These may partially or completely occlude the common duct.

It is the object of most of the special tests of liver function to aid in segregating this group from uncomplicated partial or complete obstructive jaundice. No test has to date proved successful in making this separation. Until such a test is devised it seems wiser to treat all patients with partial or complete obstructive jaundice as if liver damage were present; namely with a protein and carbohydrate diet and administration of lipotropics, vitamins including Vitamin K, as necessary to maintain normal prothrombin level as routine prior to operation.

SAMUEL WEISS, M.D., F.A.C.G.

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and
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18, 19, 20 OCTOBER 1956

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Those attending the Convention are urged to take advantage of the time in between the presentation of papers and sessions, to visit the technical exhibits and become acquainted with the many new products and new equipment on display.

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PEARCE, JOHN M., Ph.B., M.D., New York, N. Y. Professor of Pathology in Surgery, Cornell University Medical College; Attending Pathologist, New York Hospital. *(p. 16).*

PORTER, MILTON R., M.D., New York, N. Y. Assistant Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgeon, Presbyterian and Babies Hospitals; Assistant Visiting Surgeon, Francis Delafield Hospital; Consulting Surgeon, Englewood and St. Albans Naval Hospitals. *(p. 15).*

PRATT, GERALD H., M.D., F.A.C.S., New York, N. Y. Associate Clinical Professor of Surgery, New York University College of Medicine; Attending Surgeon and Chief of the Vascular Clinic, St. Vincent's Hospital. *(p. 23).*

PRATT, JOSEPH H., M.D., Boston, Mass. (deceased). Professor of Medicine (Emeritus), Tufts University Medical School; Physician-In-Chief, Pratt Diagnostic Hospital. *(p. 15).*

RATNER, BRET, M.D., New York, N. Y. Professor of Clinical Pediatrics and Director of Pediatric Allergy, New York Medical College and Flower-Fifth Avenue Hospital. *(p. 21).*

RICH, MARILYN, A.B., New York, N. Y. Research Assistant, Gastroenterology Research Laboratory, New York Medical College. *(p. 20).*

RIPSTEIN, CHARLES B., M.D., F.A.C.S., F.R.C.S., F.A.C.G., New York, N. Y. Professor of Surgery, Albert Einstein College of Medicine of Yeshiva University. *(pp. 10, 24).*

ROBINSON, EDWARD, M.D., Brooklyn, N. Y. Clinical Assistant, State University of New York College of Medicine at New York City; Assistant Physician, Maimonides Hospital. *(p. 16).*

ROTTENBERG, LOUIS A., M.D., New York, N. Y. Associate in Radiology, College of Physicians and Surgeons, Columbia University; Associate in Radiology, Columbia-Presbyterian Medical Center. *(p. 15).*

VISIT THE EXHIBITS

ROUSSELLOT, LOUIS M., A.B., M.D., M.S., (Surg.), Med. Sc.D. (Surg.), New York, N. Y. Professor of Clinical Surgery, New York University College of Medicine; Director of Surgery, St. Vincent's Hospital. *(p. 13).*

RUZICKA, FRANCIS F., Jr., A.B., M.D., New York, N. Y. Clinical Professor of Radiology, New York University College of Medicine; Director of Radiology, St. Vincent's Hospital. *(p. 13).*

SCHWARTZ, SAUL A., M.D., F.A.C.G., New York, N. Y. Associate in Internal Medicine and Gastroenterology, New York Medical College; Associate Attending, Flower-Fifth Avenue and Metropolitan Hospitals. *(p. 11).*

SHAIKEN, JOSEPH, Sc.M., M.D., F.A.C.G., Milwaukee, Wisc. Associate Professor of Medicine, Marquette University Medical School; Chief, Department of Internal Medicine and Chairman, Department of Gastroenterology, Milwaukee County Hospital. *(p. 20).*

SHEHADI, WILLIAM H., M.D., New York, N. Y. Professor of Radiology and Director of Department, New York Polyclinic Medical School and Hospital. *(p. 22).*

SHOOKHOFF, HOWARD B., A.B., M.D., D.T.M. & H. (London), New York, N. Y. Assistant Professor of Tropical Medicine, College of Physicians and Surgeons, Columbia University; Associate Professor of Preventive Medicine, Albert Einstein College of Medicine of Yeshiva University. *(p. 21).*

SNAPPER, I., M.D., Ph. D., F.A.C.G. (Hon.), Brooklyn, N. Y. Director of Medical Education, Beth-El Hospital. *(p. 18).*

SPEER, FRANCIS D., M.D., New York, N. Y. Professor of Pathology and Clinical Pathology, New York Medical College. *(p. 11).*

SPELLBERG, MITCHELL A., B.S., M.S., M.D., F.A.C.P., F,A.C.G., Chicago, Ill. Associate Professor of Clinical Medicine, University of Illinois School of Medicine; Attending Physician, Michael Reese Hospital; Consultant Gastroenterologist, Veterans Administration Hospital, Chicago. *(p. 22).*

STARK, STANLEY, M.D., F.A.C.G., Brooklyn, N. Y. Associate Physician, Kings County Hospital. *(p. 9).*

STEPHANSON, LOUKIA, A.B., New York, N. Y. Research Assistant, Gastroenterology Research Laboratory, New York Medical College. *(p. 20).*

STERLING, JULIAN A., A.B., M.D., M.Med.Sc., Sc.D., F.A.C.G., Philadelphia, Pa. Assistant Professor of Surgery, Graduate School of Medicine, University of Pennsylvania; Staff Surgeon, Albert Einstein Medical Center. *(p. 22).*

TRACKTIR, PACK, Ph.D., Houston, Texas. *(p. 21).*

WANGENSTEEN, OWEN H., B.A., M.D., Ph.D., Minneapolis, Minn. Professor and Chairman, Department of Surgery, University of Minnesota, School of Medicine. *(p. 18).*

WIRTS, C. WILMER, B.S., M.D., F.A.C.G., Philadelphia, Pa. Associate Professor of Medicine and Head, Division of Gastroenterology, Jefferson Medical College and Hospital. *(p. 20).*

WOLF, BERNARD S., M.D., B.S., New York, N. Y. Associate Clinical Professor, Columbia University; Director, Department of Radiology, The Mt. Sinai Hospital. *(p. 18.)*

ZAMCHECK, NORMAN, M.D., Boston, Mass. Instructor in Medicine, Harvard Medical School; Research Associate, Boston University Medical School; Boston City and Long Island Hospitals. *(p. 23).*

Business Sessions

SATURDAY, 13 OCTOBER 1956

All Day

Various committee meetings at times and places to be arranged by committee chairmen.

SUNDAY, 14 OCTOBER 1956

9:00 A.M.

Annual Meeting of the Board of Trustees—Vanderbilt Suite #3.

1:00 P.M.

Board of Trustees Luncheon—Vanderbilt Suite #4 and 5.

3:00 P.M.

Annual Meeting of the American College of Gastroenterology—Suite E and F.

6:30 P.M.

CONVOCATION: Presentation of Certificates—Grand Ballroom.
See special program.

8:30 P.M.

Buffet supper—Madison Room.

MONDAY, 15 OCTOBER 1956

4:00 P.M.

Meeting of the Credentials Committee—Suite E and F.

TUESDAY, 16 OCTOBER 1956

4:00 P.M.

Annual Meeting of the Board of Governors—Suite E and F.

WEDNESDAY, 17 OCTOBER 1956

12:30 P.M.

Luncheon meeting of the Board of Trustees—Suite E and F.

VISIT THE EXHIBITS

FIRST SESSION

MONDAY MORNING, 15 OCTOBER 1956

8:30 A.M. *Coffee and doughnuts will be served in the Exhibit Area with the compliments of William H. Rorer, Inc.*

James T. Nix, M.D., F.A.C.G., President, American College of Gastroenterology, presiding.

9:00 A.M.

1. "Effective Inhalation Analgesia in Gastroscopy".

Speakers

Dr. Milton J. Matzner, Brooklyn, N. Y., Dr. Stanley Stark, Brooklyn, N. Y. and Dr. Irving M. Pallin, Brooklyn, N. Y. (By invitation).

9:20 A.M.

Discusser

Dr. Jerome Weiss, New York, N. Y.

9:30 A.M.

2. "Precipitating Factors in the Development of Hepatic Coma".

Speaker

Dr. A. I. Friedman, Hackensack, N. J.

9:50 A.M.

Discusser

Dr. Stanley H. Craig, New York, N. Y.

10:00 A.M. Recess to visit the commercial, technical and scientific exhibits.

VISIT THE EXHIBITS

10:30 A.M.

3. PANEL DISCUSSION ON DISEASES OF THE ESOPHAGUS

Staff of the Albert Einstein College of Medicine, Yeshiva University.

Moderator

DR. CHARLES B. RIPSTEIN, New York, N. Y.

Participants

DR. IRWIN ARIAS, New York, N. Y. (By invitation), Medicine.
DR. ANTHONY DANZA, New York, N. Y. (By invitation), Surgery.
DR. MILTON ELKIN, New York, N. Y. (By invitation), Radiology.
DR. ALFRED ANGRIST, New York, N. Y. (By invitation), Pathology.

12:00 Noon—Question and answer period.

12:30 P.M.

LUNCHEON—Sponsored by Burton, Parsons & Co.
(admission by card only, to be obtained at the registration desk).

Speaker to be announced.

SECOND SESSION

MONDAY AFTERNOON, 15 OCTOBER 1956

FRANK J. BORRELLI, M.D., F.A.C.G., Vice-President, American College of Gastroenterology, presiding.

2:00 P.M.

4. "Studies of the Unknown Factor in Duodenal Ulcer".

Speaker

DR. MAXWELL BERRY, Atlanta, Ga.

2:20 P.M.

Discussers

DR. MAX CAPLAN, Meriden, Conn.
DR. PAUL L. SHALLENBERGER, Sayre, Pa.

2:30 P.M.

5. "Experience with Short-Term Intensive Anticholinergic Therapy of Peptic Ulcer".

Speakers

DR. HARRY BAROWSKY, New York, N. Y.; DR. JACOB LISTER, New York, N. Y. and DR. SAUL A. SCWARTZ, New York, N. Y.

2:50 P.M.

Discussers

DR. SAMUEL A. OVERSTREET, Louisville, Ky.
DR. ROBERT R. BARTUNEK, Cleveland, Ohio.

3:00 P.M. Recess to visit the commercial, technical and scientific exhibits.

3:30 P.M.

6. PANEL DISCUSSION ON DISEASES OF THE STOMACH AND DUODENUM

Staff of the New York Medical College.

Moderator

DR. LINN J. BOYD, New York, N. Y.

Participants

DR. GEORGE B. JERZY GLASS, New York, N. Y., Medicine.
DR. RALPH COLP, New York, N. Y. (By invitation), Surgery.
DR. FRANK J. BORRELLI, New York, N. Y., Radiology.
DR. FRANCIS D. SPEER, New York, N. Y. (By invitation), Pathology.

5:00 P.M.—Question and answer period.

VISIT THE EXHIBITS

THIRD SESSION

TUESDAY MORNING, 16 OCTOBER 1956

8:30 A.M. *Coffee and doughnuts will be served in the Exhibit Area with the compliments of William H. Rorer, Inc.*

HENRY J. BAKER, M.D., F.A.C.G., Vice-President, American College of Gastroenterology, presiding.

9:00 A.M.

1. "Glutamic Acid in the Treatment of Hepatic Coma and its Relationship to Blood Ammonia Levels".

Speakers

DR. NATHAN W. CHAIKIN, New York, N. Y. and DR. MAX KONIGSBERG, New York, N. Y.

9:20 A.M.

Discussers

DR. EMANUEL M. RAPPAPORT, Jamaica, N. Y.
DR. SAMUEL L. IMMERMAN, Philadelphia, Pa.

9:30 A.M.

8. "The Status of ACTH and Cortisone in Gastroenterology".

Speaker

DR. MURREL H. KAPLAN, New Orleans, La.

9:50 A.M.

Discusser

DR. EDWARD J. NIGHTINGALE, New York, N. Y.

10:00 A.M. Recess to visit the commercial, technical and scientific exhibits.

VISIT THE EXHIBITS

10:30 A.M.

9. PANEL DISCUSSION ON ESOPHAGEAL VARICES—PORTAL HYPERTENSION

Staff of the New York University College of Medicine.

Moderator

DR. HIRSCH R. LIEBOWITZ, New York, N. Y. (By invitation).

Participants

DR. CARL H. GREENE, Brooklyn, N. Y. (By invitation), Medicine.
DR. LOUIS M. ROUSSELOT, New York, N. Y. (By invitation), Surgery.
DR. FRANCIS F. RUZICKA, JR., New York, N. Y. (By invitation), Radiology.

12:00 Noon—Question and answer period.

FOURTH SESSION

TUESDAY AFTERNOON, 16 OCTOBER 1956

JOSEPH SHAIKEN, M.D., F.A.C.G., Vice-President, American College of Gastroenterology, presiding.

2:00 P.M.

10. "The Present Management of Ulcerative Colitis with Special Emphasis on Sprue Diet".

Speaker

DR. HENRY A. MONAT, Washington, D. C.

2:20 P.M.

Discusser

DR. JACOB J. WEINSTEIN, Washington, D. C.

2:30 P.M.

11. "Intussusception in Infants and Children".

Speaker

DR. HARRY A. OBERHELMAN, Chicago, Ill.

2:50 P.M.

Discussers

DR. LAWRENCE B. SLOBODY, New York, N. Y. (By invitation).
DR. WALTER L. MERSHEIMER, New York, N. Y.

VISIT THE EXHIBITS

3:00 P.M. Recess to visit the commercial, technical and scientific exhibits.

3:30 P.M.

12. PANEL DISCUSSION ON DISEASES OF THE COLON

Staff of the State University of New York, College of Medicine at New York City.

Moderator

DR. PERRIN H. LONG, Brooklyn, N. Y. (By invitation).

Participants

DR. SIDNEY M. FIERST, Brooklyn, N. Y., Medicine.
DR. IRVING M. ENQUIST, Brooklyn, N. Y. (By invitation), Surgery.
DR. HARRY C. MELLINS, Brooklyn, N. Y. (By invitation), Radiology.
DR. PATRICK M. FITZGERALD, Brooklyn, N. Y. (By invitation), Pathology.

5:00 P.M.—Question and answer period.

7:30 P.M.

ANNUAL BANQUET—PALM TERRACE SUITE, The Roosevelt, New York, N. Y.

FIFTH SESSION

WEDNESDAY MORNING, 17 OCTOBER 1956

8:30 A.M. *Coffee and doughnuts will be served in the Exhibit Area with the compliments of William H. Rorer, Inc.*

C. WILMER WIRTS, M.D., F.A.C.G., Vice-President, American College of Gastroenterology, presiding.

9:00 A.M.

13. "Histoplasmosis and the Gastroenterologist".

Speaker

DR. DONALD C. COLLINS, Hollywood, Calif.

9:20 A.M.

Discusser

DR. FRED E. MANULIS, Palm Beach, Fla.

VISIT THE EXHIBITS

9:30 A.M.

14. "Single Layer Intestinal Anastomosis, Results and Technic".

Speaker

DR. CHRISTOPHER A. BELING, Montclair, N. J.

9:50 A.M.

Discusser

DR. WALTER SHRINER, Springfield, Ill.

10:00 A.M. Recess to visit the commercial, technical and scientific exhibits.

10:30 A.M.

15. PANEL DISCUSSION ON DISEASES OF THE SMALL INTESTINE

Staff of the College of Physicians and Surgeons, Columbia University.

Moderator

DR. MICHAEL J. LEPORE, New York, N. Y. (By invitation).

Participants

DR. THOMAS ALMY, New York, N. Y. (By invitation), Medicine.
DR. MILTON PORTER, New York, N. Y. (By invitation), Surgery.
DR. LOUIS A. ROTTENBERG, New York, N. Y. (By invitation), Radiology.
DR. RAFFAELE LATTES, New York, N. Y. (By invitation), Pathology.

12:00 Noon—Question and answer period.

SIXTH SESSION

WEDNESDAY AFTERNOON, 17 OCTOBER 1956

LOUIS OCHS, JR., M.D., F.A.C.G., Chairman Board of Governors, American College of Gastroenterology, presiding.

2:00 P.M.

16. "The Urinary Lipase Test as an Aid in the Diagnosis of Carcinoma of the Pancreas".

Speakers

DR. M. M. NOTHMAN, Boston, Mass. (By invitation), DR. JOSEPH H. PRATT* Boston, Mass. (By invitation) and DR. ALLAN D. CALLOW, Boston, Mass. (By invitation).

[*Deceased]

VISIT THE EXHIBITS

2:20 P.M.

Discussers

Dr. Alfonso A. Lombardi, New York, N. Y.
Dr. Emanuel W. Lipschutz, Brooklyn, N. Y.

2:30 P.M.

17. "Steatorrhea".

Speakers

Dr. Sidney M. Fierst, Brooklyn, N. Y. and Dr. Edward Robinson, Brooklyn, N. Y.

2:50 P.M.

Discussers

Dr. L. Pulsifer, Rochester, N. Y.
Dr. William W. Abrams, Kansas City, Kansas.

3:00 P.M. Recess to visit the commercial, technical and scientific exhibits.

3:30 P.M.

18. PANEL DISCUSSION ON DISEASES OF THE GALLBLADDER AND PANCREAS

Staff of the Cornell University Medical College.

Moderator

Dr. William A. Barnes, New York, N. Y. (By invitation).

Participants

Dr. Michael Lake, New York, N. Y. (By invitation), Medicine.
Dr. Mary Ann Payne, New York, N. Y. (By invitation), Medicine.
Dr. William F. Nickel, Jr., New York, N. Y. (By invitation), Surgery.
Dr. John A. Evans, New York, N. Y. (By invitation), Radiology.
Dr. John Pearce, New York, N. Y. (By invitation), Pathology.

5:00 P.M.—Question and answer period.

VISIT THE EXHIBITS

SEVENTH SESSION

WEDNESDAY EVENING, 17 OCTOBER 1956

ANTHONY BASSLER, M.D., F.A.C.G., Honorary President, American College of Gastroenterology, presiding.

8:00 P.M.

Presentation of the Winning Paper in the 1956 Ames Award Contest.

8:30 P.M.

MOTION PICTURE PROGRAM

1. **"Liver Biopsy with Vim Silverman Needle". (18 min.)**

   DR. CHARLES H. BROWN AND DR. ARTHUR M. CLARK, Cleveland, Ohio.

2. **"The Termination of the Bile Duct". (15 min.)**

   DR. JULIAN A. STERLING, Philadelphia, Pa.

3. **"Operative Clinic on Jaundice". (42 min.)**

   DR. FRANCIS D. MOORE, Boston, Mass.

4. **"Hemorrhoidectomy—An Inside Job". (18 min.)**

   DR. PAUL V. VAN DYKE, Suffern, N. Y.

5. **"The Technic of Proctosigmoidoscopy and Its Role in the Cancer Detection Program". (21 min.)**

   DR. WILLIAM C. BERNSTEIN, St. Paul, Minn.

COURSE IN POSTGRADUATE GASTROENTEROLOGY

SURGICAL COORDINATOR AND CO-CHAIRMAN

OWEN H. WANGENSTEEN, B.A., M.D., Ph.D., Minneapolis, Minn.

MEDICAL COORDINATOR AND CO-CHAIRMAN

I. SNAPPER, M.D., Ph.D., F.A.C.G. (Hon.), Brooklyn, N. Y.

FIRST SESSION

THURSDAY MORNING, 18 OCTOBER 1956

ARTHUR A. KIRCHNER, M.D., F.A.C.G., President, American College of Gastroenterology, presiding.

9:00 A.M.

Address of Welcome—

9:05 A.M.

1. "Lesions of the Oral Cavity".

Speaker
DR. LESTER R. CAHN, New York, N. Y.

9:35 A.M.

2. "Roentgen Examination of the Esophagus".

Speaker
DR. BERNARD S. WOLF, New York, N. Y.

10:05 A.M.

3. "Chylothorax and Chylous Ascites: Classification, Pathogenesis, Diagnosis and Management".

Speakers
DR. JAMES T. NIX, New Orleans, La. and DR. MATTHEW ALBERT, New Orleans, La.

VISIT THE EXHIBITS

10:35 A.M. Recess to visit the commercial, technical and scientific exhibits. (Exhibits close at 2:00 P.M.).

11:05 A.M.

4. "Medical Management of Peptic Ulcer".

Speaker
DR. CHARLES A. FLOOD, New York, N. Y.

11:35 A.M.

5. "Surgical Management of Gastric Ulcer".

Speaker
DR. RALPH COLP, New York, N. Y.

SECOND SESSION

THURSDAY AFTERNOON, 18 OCTOBER 1956

This entire session will be held at the Metropolitan Medical Center, 97th St. and First Ave. The session will be in the auditorium on the sixth floor.

LINN J BOYD, M.D., F.A.C.G. (Hon.) Honorary Fellow, American College of Gastroenterology, presiding.

2:00 P.M.

GASTROENTEROLOGICAL CLINICAL CONFERENCE

Chairman
DR. HARRY BAROWSKY

Participants

The Faculty Members of New York Medical College and the Course Moderators.

3:30 P.M. Recess.

VISIT THE EXHIBITS

3:45 P.M.

6. "The Postbulbar Duodenal Ulcer".

Speakers

DR. JOSEPH SHAIKEN, Milwaukee, Wisc. and DR. HARRY J. KANIN, Milwaukee, Wisc.

4:15 P.M.

7. "Management of Gastrointestinal Bleeding".

Speaker

DR. C. WILMER WIRTS, Philadelphia, Pa.

4:45 P.M.

8. "Massive Hemorrhage of the Upper Gastrointestinal Tract: The Indications for and the Surgical Procedure of Choice".

Speaker

DR. J. WILLIAM HINTON, New York, N. Y.

THIRD SESSION

FRIDAY MORNING, 19 OCTOBER 1956

This session and all subsequent sessions will again be held at The Roosevelt.

THEODORE S. HEINEKEN, M.D., F.A.C.G., Secretary, American College of Gastroenterology, presiding.

9:00 A.M.

9. "Paper Electrophoretic Analysis of Gastric Juice in Health and Disease".

Speakers

DR. GEORGE B. JERZY GLASS, New York, N. Y.; LOUKIA STEPHANSON, New York, N. Y. and MARILYN RICH, New York, N. Y.

VISIT THE EXHIBITS

9:30 A.M.

10. "Clinical Aspects of Parasitic Infections of the Gastrointestinal Tract".

Speaker

DR. HOWARD B. SHOOKHOFF, New York, N. Y.

10:00 A.M.

11. "Diagnostic Laboratory Procedures in Diseases of the Stomach and Intestines".

Speaker

DR. MAURICE BRUGER, New York, N. Y.

10:30 A.M. Recess.

10:45 A.M.

12. "Personality as a Factor in the Study of Autonomic Function".

Speakers

DR. RALPH EICHHORN, Houston, Texas and DR. JACK TRACKTIR, Houston, Texas.

11:15 A.M.

13. "Denatured Food Diet in Allergy".

Speaker

DR. BRET RATNER, New York, N. Y.

12:00 Noon

BUFFET LUNCHEON (Admission by card only).

VISIT THE EXHIBITS

FOURTH SESSION

FRIDAY AFTERNOON, 19 OCTOBER 1956

SAMUEL WEISS, M.D., F.A.C.G., Chairman, Editorial Board, American College of Gastroenterology, presiding.

2:00 P.M.

14. "Roentgen Studies of the Biliary Tract: An Evaluation of Recent Contributions".

Speaker
DR. WILLIAM H. SHEHADI, New York, N. Y.

2:30 P.M.

15. "Carcinomatous Biliary Obstruction".

Speaker
DR. CLARENCE DENNIS, Brooklyn, N. Y.

3:00 P.M.

16. "Individualization in Management of Obstructive Jaundice".

Speaker
DR. JULIAN A. STERLING, Philadelphia, Pa.

3:30 P.M. Recess.

3:45 P.M.

17. "Liver Functional Tests: Their Clinical Significance with Special Emphasis on Elevations of Alkaline Phosphatase and Cholesterol".

Speaker
DR. MITCHELL A. SPELLBERG, Chicago, Ill.

4:15 P.M.

18. "Diagnosis and Treatment of Splenomegaly".

Speaker
DR. WILLIAM DAMESHEK, Boston, Mass.

VISIT THE EXHIBITS

FIFTH SESSION

SATURDAY MORNING, 20 OCTOBER 1956

WILLIAM C. JACOBSON, M.D., F.A.C.G., Trustee, American College of Gastroenterology, presiding.

9:00 A.M.

19. "Recent Developments in Understanding of Thorazine Jaundice".

Speakers

DR. NORMAN ZAMCHECK, Boston, Mass. and DR. IRWIN ARIAS, New York, N. Y.

9:30 A.M.

20. "The Laboratory Diagnosis of Pancreatic Disease: Secretin Test".

Speakers

DR. DAVID A. DREILING, New York, N. Y. and DR. HENRY D. JANOWITZ, New York, N. Y.

10:00 A.M.

21. "Visceral Manifestations of Occlusive Disease of the Intestinal Blood Vessels".

Speaker

DR. GERALD H. PRATT, New York, N. Y.

10:30 A.M. Recess.

10:45 A.M.

22. "Cultural Studies of the Human Stool and Sensitivity Tests".

Speakers

DR. DAVID C. DITMORE, Boston, Mass. and DR. HOWARD LIND, Boston, Mass.

VISIT THE EXHIBITS

11:15 A.M.

23. "Surgical Management of Polyps of the Colon and Rectum".

Speaker

DR. IRVING F. ENQUIST, Brooklyn, N. Y.

SIXTH SESSION

SATURDAY AFTERNOON, 20 OCTOBER 1956

LYNN A. FERGUSON, M.D., F.A.C.G., Secretary-General, American College of Gastroenterology, presiding.

2:00 P.M.

24. "Antibiotics and Colon Surgery".

Speaker

DR. ISIDORE COHN, JR., New Orleans, La.

2:30 P.M.

25. "Surgical Treatment of Ulcerative Colitis".

Speaker

DR. CHARLES B. RIPSTEIN, New York, N. Y.

3:00 P.M.

26. "Anorectal Diseases: Diagnosis and Office Management".

Speakers

DR. SYLVAN D. MANHEIM, New York, N. Y. and DR. RICHARD ALEXANDER, New York, N. Y.

3:30 P.M.

27. "Non-inflammatory Proctalgias and Allied Anorectal Proctalgias".

Speaker

DR. EMIL GRANET, New York, N. Y.

VISIT THE EXHIBITS

SCIENTIFIC EXHIBITS

BOOTH A **"The Trigger Area in Abdominal Disturbances".**
DR. JACOB MELNICK, Brooklyn, N. Y.

In abdominal disturbances a somatic component is consistently present which may aggravate and prolong the condition. It is most commonly present in the form of hypersensitive zones within the myofascial tissue and is known as a trigger area. Trigger areas persist after the original disturbance has subsided and may by themselves become a cause of symptoms and physical findings. Illustrations are presented showing the specific trigger areas and the physical signs and symptoms associated with them. Treatment is described and illustrated. The results of treatment of such trigger areas in over one hundred patients with longstanding and refractory abdominal disturbances is presented and their importance as a diagnostic factor is stressed.

BOOTH B **"Intravenous Cholangiography".**
DR. ADOLPH A. ADAMS, New York, N. Y.

The exhibit will consist of two parts. 1. Radiograms illustrating the technic and application of intravenous cholangiography. Large series of films also spot films illustrating pathological conditions. 2. Motion picture studies of the biliary tract.

BOOTH C **"Partial Gastrectomy with or Without Vagus Resection for Duodenal Ulcer".**
DR. LOUIS T. PALUMBO, DR. THEODORE T. MAZUR and DR. BERNARD J. DOYLE, Des Moines, Iowa.

The exhibit presents indications and the percentage of patients with duodenal ulcer receiving surgery. The incision and basic technic used in 250 cases are illustrated by transparencies in color. The morbidity and mortality are compared and other factors considered in final evaluation. Comparative changes in the gastrointestinal motor functions are presented in roentgenograms. The results in both groups and the evaluation of patients for combined partial gastrectomy and vagus resection are presented.

BOOTH D **"Surgery of the Gallbladder and Bile Ducts".**
DR. JOHN L. MADDEN, DR. WILLIAM J. MCCANN and DR. JOHN M. LORE, JR., New York, N. Y.

In this exhibit colored photographic illustrations of the experimental data relative to the reconstruction of the common bile duct without the use of stents is shown. These data are correlated with similar data in the human. There are also artist illustrations depicting the surgical technic for cholecystectomy and common duct exploration. In addition there are colored photographs of the surgical specimens showing the various types of gallstones and inflammatory lesions of the gallbladder. Colored photographs of injected human cadaver specimens to illustrate the anatomy of the gallbladder and bile ducts will also be shown.

BOOTH E **"Usefulness of Chlorpromazine in a Variety of Clinical Problems".**
DR. CHARLES E. FRIEDGOOD, Brooklyn, N. Y.

The exhibit summarizes our experience with chlorpromazine in more than 400 patients. It includes results obtained. 1. in control of intractable hiccoughs, 2. in control of persistent nausea and vomiting, 3. to relieve pain with and without narcotics and 4. in various gastro-intestinal psychosomatic diseases. Charts, tables, photographs and case histories will be shown.

BOOTH F **"Diagnosis by Gastroscopy—Hemorrhagic Lesions in the X-ray Negative Stomach".**

DR. EMMANUEL DEUTSCH and DR. DANIEL L. SHAW, JR., Boston, Mass.

When a definite bleeding point during gastric hemorrhage is not discovered by x-ray, then gastroscopy can be of considerable help. This exhibit includes slides of drawings and photomicrographs showing acute mucosal ulceration and multiple erosions, sliding hiatus hernia, a small broad-based polyp, gastric purpura, anastomotic ulcer, ectasia of gastric mucosa, and a circumscribed carcinomatous ulcer. It also illustrates the value of gastric biopsies and aspiration taken during gastroscopy. The mechanism and clinical features of gastric hemorrhage in the stomach, that is normal on x-ray, are presented together with illustrative cases.

BOOTH G **"Gastric Acid Depression".**

DR. ARTHUR P. KLOTZ, Kansas City, Kans.

The exhibit indicates the depression of free acid in the stomach by a new anticholinergic agent which is unique because of its minimal side-effects. Demonstrated is the type of gastric analysis performed in the evaluation of the medication with a brief description of the method used. Measurement of decrease in acid is based upon the calculation of milliequivalents of acid before and after gastric instillation of the drug. A decrease to one-half or less than one-half of the basal acidity was considered significant.

Shown graphically are the results in 40 per cent of the patients who developed total anacidity and the duration of that anacidity.

The summary describes the effects on acid secretion in *all* of the patients tested.

BOOTH H **"Treatment of Gastric Cancer".**

Memorial Cancer Center, New York, N. Y.

Gastric Service: DR. GEORGE T. PACK, DR. GORDON MCNEER, DR. ROBERT BOOHER, DR. THEODORE R. MILLER, DR. LEMUEL BOWDEN, DR. RICHARD BRASFIELD, DR. CHARLES MCPEAK and DR. JOSEPH FORTNER

Experimental Physiology: DR. HENRY T. RANDALL, DR. KATHLEEN ROBERTS, DR. MORTON SCHWARTZ and DR. ALLEN LEY

Pathology Department: DR. DOUGLAS SUNDERLAND and DR. LOUIS ORTEGA

The exhibit covers three phases in the treatment of cancer of the stomach:

1. Pathologic studies based on autopsy and investigation of especially cleared surgical specimens for lymph node distribution of metastases. As a result, certain conclusions are drawn regarding surgical technic.

2. Metabolic changes in humans after total gastrectomy.

3. End-results of treatment.

BOOTH I **"The Malignant Carcinoid Syndrome".**

DR. ALBERT SJOERDSMA and DR. LUTHER L. TERRY, Bethesda, Md.

This exhibit consists of three panels:

CENTER PANEL: lists clinical features of the disorder viz. vasomotor disturbances, cardiac involvement, broncheo constriction, hematomegaly, and intestinal hypermotility. Organ involvement is shown in an artist's model of a patient and flushing of the skin is illustrated by color transparencies.

LEFT PANEL: shows the alterations in tryptophan metabolism and proof of precursor relationship of tryptophan to serotonin in man. Tables show high content of serotonin in a carcinoid tumor, elevated blood serotonin in patients and increased urinary excretion of serotonin metabolites.

RIGHT PANEL: gives certain laboratory features and correlation of clinical findings with metabolic derangement.

BOOTH J **"Effect of Anticholinergic Drugs on Normal and Abnormal Gastrointestinal Motility".**

DR. WOLFGANG F. VOGEL, Paterson, N. J.

One hundred twenty gastrointestinal series were performed on 48 patients using various anticholinergic agents and controls. Representative x-ray series are shown.

The barium meal technic presents the most physiologic and standardized approach to the study of gastrointestinal motility. Motility is not affected by instrumentation, as in esophagoscopy; or by pressure of foreign bodies, as balloon, which may alter further the normal variation in motility.

Absorption time of various anticholinergic drugs varies and has not been widely studied. This is probably the largest single source of error in studies of this nature.

In control studies, the majority of normal subjects had gastric emptying between 1 and 2½ hours after ingestion of barium. Greater variability existed in peptic ulcer patients.

Anticholinergic drugs cause decreased tone of gastrointestinal musculature as manifested by delayed gastrointestinal transit of barium and widening of the lumen of the small bowel. Widening of the gastric lumen is suggested but it is not conclusive.

Abnormally prolonged gastric emptying was shortened by use of anticholinergic drugs, while rapid gastric emptying was delayed. Small intestinal transit time was uniformly prolonged in both normal and abnormal conditions.

BOOTH K **"Radiologic Diagnosis of Hiatus Hernia".**

DR. LESLIE K. SYCAMORE, Hanover, N. H.

The anatomy and physiology of the lower esophagus are discussed and illustrated. A classification of hiatus hernia is presented and the different types shown. Difficulties in diagnosis and points of differential diagnosis are exemplified, including the lower esophageal ring. Complications of hiatus hernia are shown. Several unanswered problems are pointed out.

TECHNICAL EXHIBITORS

(Those attending the Convention sessions are urged to take advantage of the time in between the presentation of papers and sessions, to visit the technical exhibits and become acquainted with many new products and new equipment on display.)

AMES COMPANY, INC., Elkhart, Ind. (Booth 14), will exhibit: *My-B-Den,* the adenine nucleotide, adenosine-5-monophosphate, found highly effective in the treatment of varicose vein complications, stasis and bursitis. *My-B-Den* preoperatively shortens the waiting period necessitated by poor tissue condition and enhances surgical results. The routine use of *Decholin* in geriatric patients has proved most beneficial. Common geriatric problems of constipation, inadequate fat digestion and improper liver function are easily overcome.

J. BEEBER CO., INC., New York, N. Y. (Booth 2). On display will be the latest type of Mattern X-ray apparatus, such as the Mattern 200 MA with 4-in-1 Spot Device. Also on display will be the new Beck-Lee Electrocardiograph.

BILHUBER-KNOLL CORP., Orange, N. J. (Booth 16). Complete information on the new analgesic *Paracodin* is available. *Paracodin* is a powerful analgesic yet essentially free from respiratory depression, as well as nausea and dizziness. *Paracodin* is indicated in acute and chronic pain. Their representatives cordially invite you to discuss the use of this analgesic as well as antispasmodic *Octin* and the sedospasmolytic *Valoctin.*

BURTON, PARSONS & COMPANY, Washington, D.C. (Booth 15). You are cordially invited to visit their booth where information, samples and literature will be available on their hydrophilic colloids, *L. A. Formula* and *Konsyl. L. A. Formula* contains 50 per cent bulk producing material dispersed in an equal amount of lactose and dextrose. *Konsyl,* on the other hand, contains 100 per cent bulk producing material and is certainly the product of choice for the obese, the diabetic, and others with restricted caloric intake. Orange juice will also be available to prove that *L. A. Formula* is unsurpassed for palatability and literally defies detection in orange juice.

THE COCA-COLA COMPANY, Atlanta, Ga. (Lounge). Ice-cold Coca-Cola will be served through the courtesy and cooperation of The Coca-Cola Bottling Company of New York and The Coca-Cola Company.

THE EDER INSTRUMENT COMPANY, Chicago, Ill. (Booth 20) will as usual display some of their latest developments in gastroscopic equipment. This year is no exception and it would be worthwhile to investigate them at Booth 20.

ENCYCLOPAEDIA BRITANNICA, New York, N. Y. (Booth 10) will exhibit the new 1956 Edition of the Encyclopaedia Britannica. This leading reference work with its 188-year history has been completely revised in an intensive effort of the last 13 years representing an investment of $4,000,000. Illustrated in color, it contains 38,149,128 words which have been either revised or rewritten with approximately 539,107 index references.

OTIS E. GLIDDEN & CO., INC., Waukesha, Wisc. (Booth 23) will exhibit New Products: *BSP Liquid* for bed sore prevention, and *Zylax* for fast, gentle laxation, are being introduced to you here. *Zymenol* and *Zymelose* are on exhibit, too. Samples are available at their booth and their representative will arrange to send the desired material to you.

VISIT THE EXHIBITS

GRAY PHARMACEUTICAL COMPANY, Newton, Mass. (Booth 1). An informative exhibit on geriatrics will be featured. Data on cerebral stimulation and protein utilization will be presented. Their Medical Service Representatives will be pleased to discuss *L-Glutavite,* a "cerebral tonic" formulated to stimulate cerebral metabolism and circulation; *Lysidox,* "the key of protein utilization" in the aged, and *Diovac,* a new concept in the treatment of constipation.

GRUNE & STRATTON, INC., New York, N. Y. (Booth 6). Mr. Martin J. Cann welcomes you to Booth 6, where you can examine such important books as: Schindler's *Synopsis of Gastroenterology;* Necheles-Kirshen's *The Physiologic Basis of Gastrointestinal Therapy;* Spellberg's *Diseases of the Liver;* Bendick's *Diagnostic Advances in Gastrointestinal Roentgenology;* Nieburg's *Cytology Technics for Office and Clinic;* Cantor and Foxe's *Psychosomatic Aspects of Surgery;* Storch's *Fundamentals of Clinical Fluoroscopy,* 2nd Revised Edition; Schinz's *Roentgen-Diagnostics, Volume IV, G-I Tract, Gynecology, Urology,* and many other timely books in your field.

J. B. LIPPINCOTT COMPANY, Philadelphia, Pa. (Booth 17) presents, for your approval, a display of professional books and journals geared to the latest and most important trends in current medicine and surgery. These publications, written and edited by men active in clinical fields and teaching, are a continuation of more than 100 years of traditionally significant publishing.

LLOYD BROTHERS, INC., Cincinnati, Ohio (Booth 24). *Doxinate,* the original preparation of dioctyl sodium sulfosuccinate, for the prevention and treatment of constipation will be featured at the Lloyd exhibit. *Doxinate,* the first fecal softener, has pioneered an entirely new approach to the restoration of normal bowel habits through the employment of its wetting action on fecal material. Competent representatives will welcome an opportunity to present the interesting data and research background which have contributed to the success of this totally new therapy.

THE MALLON CHEMICAL CORPORATION, subsidiary of the DOHO CHEMICAL CORPORATION, New York, N. Y. (Booth 4), makers of *Auralgan, New Otosmosan,* and *Rhinalgan,* are pleased to exhibit *Rectalgan,* the liquid topical anesthesia for relief of pain and itching in hemorrhoids and pruritus; following perineal suturing in obstetrical and gynecological work, and for many other uses in pre- and postoperative cases. *Dermoplast,* in aerosol freon propellent spray for fast relief of surface pain, itching, burns and abrasions. Also for obstetrical and gynecological use.

THE NATIONAL DRUG COMPANY, Philadelphia, Pa. (Booth 19).

PICKER X-RAY CORPORATION, White Plains, N. Y. (Booths 26-27), will display a complete 200 M.A. Radiographic and Fluoroscopic unit. In addition to the tilting table, the unit includes a spot film device for instantaneous radiography during examination of the gastrointestinal tract. You are cordially invited to discuss your x-ray problems with the technical personnel on duty.

THE PURDUE FREDERICK COMPANY, New York, N. Y. (Booth 5), will feature: *Senokot* Tablets and Granules—new non-bulk, non-irritating constipation corrective acting selectively on the parasympathetic (Auerbach's) plexus in the large bowel, physiologically stimulating the neuromuscular defecatory reflex. *Pre-Mens* – the multidimensional premenstrual tension therapy. *Somative* – clinically proven to promote weight gain, increase appetite and reduce hyperactivity and restlessness. *Sippyplex* – the modern comprehensive therapy for peptic ulcer.

VISIT THE EXHIBITS

WILLIAM H. RORER, INC., Philadelphia, Pa. (Booth 21) presents: *Probutylin*—(Procaine Isobutyrate-Rorer) a clinically proven drug for control of nausea, vomiting, gastritis and many other undesirable reflex manifestations of gastrointestinal origin. *Maalox*—(Magnesium Aluminum Hydroxide) a nonconstipating, pleasant tasting antacid for peptic ulcer, gastritis, and heartburn in pregnancy. *Ascriptin*—An ethically-promoted buffered aspirin which raises plasma salicylate level to more than twice that achieved by an equal dose of plain acetylsalicylic acid. The action is more rapid and of greater duration. Gastric distress seldom occurs. Indicated for pain relief in myositis, rheumatoid arthritis, headache and all uses for which salicylates are administered.

SANDOZ PHARMACEUTICALS, Hanover, N. J. (Booth 12) cordially invites you to visit their display of: *Belladenal*—Antispasmodic sedative for the control of hypermotility with pain and hypersecretion of the intestinal tract. *Cafergot*—Available in oral and rectal form for effective control of head pain in migraine and other vascular headaches. *Fiorinal*—A new approach to therapy of tension headaches and other head pain due to sinusitis and myalgia. Any of their representatives in attendance will gladly answer questions about these and other Sandoz products.

SCHENLEY LABORATORIES, INC., New York, N. Y. (Booth 13). All members and guests—welcome to the Schenley Laboratories booth! Prominently featured is *Titralac* and *Titralac-SP*, the delicious and "different" antacid that inactivates excess acid like milk. Displayed also is *Sedamyl*, the calming, nonhypnotic product, especially adapted for industrial use. *Sedamyl* is not a barbiturate; the worker remains placid, yet alert. *Dorbane* utilizes the chemical principle of Cascara for the chronically constipated. *MorCal* is a pleasant-tasting high calorie food supplement fortified with Vitamins B_1 and B_{12}, prepared from vegetable products and skim milk solids.

SCHERING CORPORATION, Bloomfield, N. J. (Booth 8). You are cordially invited to visit the Schering exhibit where new therapeutic developments will be featured. Schering representatives will be present to welcome you and to discuss with you these products of their manufacture.

E. R. SQUIBB & SONS, New York, N. Y. (Booth 9) has long been a leader in the development of new therapeutic agents for prevention and treatment of disease. The results of their diligent research are available to the Medical Profession in new products or improvements in products already marketed. At Booth 9, they are pleased to present up-to-date information on these advances for your consideration.

U. S. VITAMIN CORPORATION, New York, N. Y. (Booth 7) Exhibit features C.V.P., an exclusive water-soluble citrus bioflavonoid compound with ascorbic acid . . . for restoring and maintaining capillary integrity. Corrects or minimizes capillary abnormality and bleeding associated with diabetes, hypertension, epistaxis, purpura, gingivitis and certain forms of gastrointestinal, rectal and vaginal bleeding. Effective therapy in habitual and threatened abortion. Used experimentally against the "common cold" and other virus infections. Professional samples and literature distributed also on their complete line of nutritional and pharmaceutical specialties.

WINTHROP LABORATORIES, New York, N. Y. (Booth 11), will exhibit: New A.P.C. with Demerol tablets for potentiated pain relief. Each tablet contains aspirin 3 grains, phenacetin 2½ grains, caffeine ½ grain with Demerol hydrochloride 30 mg. A.C.P. with Demerol tablets combine marked potentiation of analgesia with mild sedation and spasmolytic action. They do not cause constipation nor interference with micturation. *Creamalin:* nonalkaline, nonabsorbable antacid.

VISIT THE EXHIBITS

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NEWS NOTES

Third Annual Convention

The Third Annual Convention of the American College of Gastroenterology will open at The Roosevelt in New York City on Sunday, 14 October 1956, with the Annual Meeting of the Board of Trustees in the morning. This will be followed by a luncheon for the Board and a continuation of the meeting.

In the afternoon, registration will take place and the Annual Meeting of the Fellowship will be held at 3:00 P.M. The Ladies Auxiliary will also have their Annual Meeting at this time.

At 6:30 P.M. the Annual Convocation Ceremony, at which time certificates will be presented to newly elected and advanced Fellows, will take place in the Grand Ballroom.

Following the Convocation, a buffet supper has been planned for those attending.

Monday morning, the Scientific Sessions will open in the Grand Ballroom, and will continue through Wednesday evening. In addition to individual papers, there will be six panel discussions, one to be presented by each of the six medical schools in New York City.

Technical and Scientific Exhibits will be open all three days and will be located on the Convention floor. The registration desk will also be on the same floor and no one will be admitted to the exhibits or the sessions without a badge.

Commencing Monday morning at 8:30 and each morning through Thursday at the same time, coffee and doughnuts will be served in the exhibit area with the compliments of William H. Rorer, Inc.

At 12:30 P.M. on Monday, 15 October, Burton, Parsons & Co. will again sponsor a luncheon for those attending with a prominent speaker scheduled to address the group.

The Annual Banquet of the College will take place on Tuesday evening, 16 October in the Palm Terrace Suite. The Ames Awards will be presented at this time and the incoming President, Dr. Arthur A. Kirchner of Los Angeles, Calif., will be invested with the insignia of office by the outgoing President, Dr. James T. Nix of New Orleans, La.

This year there will be no formal Wednesday evening session. The winning paper in the Ames Award Contest for 1956 will be given at 8:00 P.M. and this will be followed by a series of interesting motion pictures on gastroenterology and allied fields.

The Program Committee, under the Chairmanship of Dr. Frank J. Borrelli, has, as usual, prepared excellent scientific meetings. Copies of the program are being mailed to the membership of the College and additional copies are available from the headquarters office, 33 West 60th Street, New York 23, N. Y.

Ladies Auxiliary Program

The Ladies Auxiliary has as usual planned an interesting and entertaining program for the Ladies and families of those attending the Convention. Full details will be sent by mail.

The tentative program is as follows:

Sunday, 14 October 1956

Registration opens at 1:00 P.M. A badge is necessary in order to visit the exhibits.

Business meeting of the Auxiliary and election of officers at 3:00 P.M.

Convocation Ceremony at 6:30 P.M.

Buffet supper 8:30 P.M.

Monday, 15 October 1956

Social get together and coffee hour at The Roosevelt at 9:30 A.M.

"New York Has Everything" a talk with Kodachrome slides in "Cinema-Scope" will be presented by Mr. R. Gerald Morris, through the cooperation of the Program Bureau of the New York Telephone Co., at 10:00 A.M.

Sightseeing tour by boat around Manhattan Island at 2:30 P.M.

The evening will be open for individual activities such as theatre, or a Nite Life tour.

Tuesday, 16 October 1956

Breakfast and program at the Charleston Gardens Restaurant of B. Altman & Co. on New York's Fifth Avenue at 9:00 A.M.

Tour of the U. N. with luncheon in the Delegates Dining Room commencing at 11:30 A.M.

Two and one-half hour bus sightseeing tour of New York City, leaving from the U. N. at 2:30 P.M.

Cocktail party and Annual Banquet of the Association at The Roosevelt at 7:00 P.M. This annual event is *informal.* Dancing and entertainment will follow the banquet. *Reservations must be made in advance.*

Wednesday, 17 October 1956

Luncheon and fashion show at The Waldorf-Astoria at 12:30 P.M.

The afternoon can be spent visiting the Museum of Modern Art.

Registration

Registration for the Convention will take place on the mezzanine floor at The Roosevelt commencing at 2:00 P.M., on Sunday, 14 October 1956. Those attending are requested to register and receive their identification badges as no one will be admitted to the exhibits or sessions without a badge.

Board of Trustees

The Annual Meeting of the Board of Trustees will be held at The Roosevelt in New York City, at 9:00 A.M., on Sunday, 14 October 1956. A luncheon for the Trustees will follow the meeting.

Annual Meeting of the American College of Gastroenterology

The Annual Meeting of the American College of Gastroenterology will be held at The Roosevelt in New York City, on Sunday afternoon, 14 October 1956 at 3:00 P.M. Election of Officers, Trustees and Governors will be held at that time.

Fellows of the College are requested to attend and participate in the business session.

Convocation Ceremony

The Convocation Ceremony, at which Honorary Fellowships, Fellowships and Associate Fellowships will be conferred and certificates presented, will take place on Sunday evening, 14 October 1956 at The Roosevelt in New York City.

All are invited to attend.

Buffet Supper

A buffet supper has been arranged to follow the Convocation on Sunday, 14 October 1956 in the Madison Room at The Roosevelt in New York City.

Tickets will be available at the registration desk and the affair will start at 8:00 P.M.

Scientific Exhibits

Dr. Michael W. Shutkin, Chairman of the Scientific Exhibit Committee, has obtained a great many excellent exhibits which will be on display in the exhibit area from Monday through Thursday.

As in the past, the committee will select the best exhibits and certificates and ribbons will be awarded.

Burton, Parsons & Co. Luncheon

Once again this year, Burton, Parsons & Co. of Washington, D. C., will sponsor the annual luncheon for those attending the Convention.

Admission will be by ticket only which may be obtained at the registration desk on the Convention floor.

Credentials Committee

The Credentials Committee will meet at The Roosevelt in New York City at 4:00 P.M. on Monday, 15 October 1956. The closing date for applications to be considered at this meeting will be 1 October 1956.

Applications received subsequent to the closing date will be held for the spring meeting of the committee.

Meeting of the Board of Governors

The Annual Meeting of the Board of Governors will be held at The Roosevelt in New York City on Tuesday, 16 October 1956 at 4:00 P.M.

A Chairman is to be elected and committees will be appointed.

Annual Banquet

The Annual Banquet of the College will take place at The Roosevelt in New York City on Tuesday evening, 16 October 1956 at 7:00 P.M. Cocktails will precede the dinner and there will be dancing and entertainment following.

Announcement and presentation of the annual Ames Awards will be made at this time. There will be no formal speakers but Dr. Arthur A. Kirchner of Los Angeles, Calif., will be installed as President.

Tickets at $10.00 per person will be available at the registration desk. The affair will be *informal* and all reservations must be made by 10:00 A.M., Tuesday, 16 October 1956.

Special Motion Picture Program

A special program of motion pictures will be shown in the Grand Ballroom of The Roosevelt Hotel in New York City, on Wednesday evening, 17 October 1956. The program is scheduled for approximately 8:30 P.M., immediately following the presentation of the Ames Award paper.

Course in Postgraduate Gastroenterology

The annual Course in Postgraduate Gastroenterology of the American College of Gastroenterology will be held at The Roosevelt in New York City on 18, 19, 20 October 1956, with an afternoon session to be held at the new Metropolitan Medical Center, 97th St. & First Ave.

The faculty giving the Course has been selected from the medical schools in New York City and adjacent areas. Dr. Owen H. Wangensteen, Professor and Chairman of the Department of Surgery, University of Minnesota Medical School and Dr. I. Snapper, Director of Medical Education, Beth-El Hospital, Brooklyn, N. Y., will again be the moderators.

Admission to the Course sessions is limited to those who hold matriculation cards indicating that they have paid their fee for the Course.

Nominating Committee Report

The Nominating Committee of the American College of Gastroenterology, consisting of Dr. Lynn A. Ferguson, Grand Rapids, Mich., Chairman; Dr. Arthur A. Kirchner, Los Angeles, Calif.; Dr. Edward G. Campbell, Memphis, Tenn.; Lester M. Morrison, Los Angeles, Calif. and Dr. Michael W. Shutkin, Milwaukee, Wisc., has submitted the following slate of candidates to be voted upon at the Annual Meeting of the College in October:

Officers

President-Elect.....C. Wilmer Wirts, M.D., Philadelphia, Pa.
1st Vice-President.....Frank J. Borrelli, M.D., New York, N. Y.
2nd Vice-President.....Joseph Shaiken, M.D., Milwaukee, Wisc.
3rd Vice-President.....Henry Baker, M.D., Boston, Mass.
4th Vice-President.....Louis Ochs, Jr., M.D., New Orleans, La.
Secretary.....Theodore S. Heineken, M.D., Bloomfield, N. J.

Board of Trustees

For 3 years:	H. Necheles, M.D., Chicago, Ill.
	Louis L. Perkel, M.D., Jersey City, N. J.
	M. E. Steinberg, M.D., Portland, Ore.
	Murrel H. Kaplan, M.D., New Orleans, La.
	Milton J. Matzner, M.D., Brooklyn, N. Y.
For 1 year:	John M. McMahon, M.D., Bessemer, Ala.

Board of Governors

District of Columbia	Henry A. Monat, M.D., Washington
Illinois	Harry A. Oberhelman, M.D., Chicago
Kentucky	Sam A. Overstreet, M.D., Louisville
Massachusetts	Charles W. McClure, M.D., Boston
Michigan	James A. Ferguson, M.D., Grand Rapids
New Jersey	Earl J. Halligan, M.D., Jersey City
Upper New York	Libby Pulsifer, M.D., Rochester
Rhode Island	William L. Leet, M.D., Providence
Tennessee	Henry G. Rudner, Sr., M.D., Memphis
Wisconsin	Robert T. McCarty, M.D., Milwaukee

ORAL EXAMINATION IN GASTROENTEROLOGY

Dr. Lowell D. Snorf, Chairman of the Sub-specialty Board of Gastroenterology of the American Board of Internal Medicine, announces that an examination will be held on 5 and 6 April 1957, at the Graduate Hospital, Philadelphia, Pa.

For additional information and applications, please write to Dr. William A. Werrell, Executive Secretary-Treasurer, American Board of Internal Medicine, 1 West Main Street, Madison 3, Wisc. No applications for this examination will be accepted after 1 March 1957.

In Memoriam

We record with profound sorrow the passing of Dr. Israel Mostkowitz of Jamaica, N. Y., Fellow of the American College of Gastroenterology. We extend our deepest sympathy to the bereaved family.

ABSTRACTS FOR GASTROENTEROLOGISTS

ESOPHAGUS

THE DIAGNOSIS, ETIOLOGY AND TREATMENT OF ESOPHAGEAL HERNIA: Porter P. Vinson, Virginia Med. Monthly 82:346 (Aug.), 1955.

Hiatal esophageal hernia is of two varieties: 1. paraesophageal, 2. short esophagus, or sliding type. All hiatal herniae are probably congenital in origin.

Surgical treatment of the sliding type of hernia is not required, as symptoms can be relieved by passing sounds over a guiding thread through the esophagus. The presence of the abnormality does not constitute hazard to life if the lumen of the esophagus is properly maintained.

If esophagitis in sliding hiatal hernia is caused by regurgitation, dilation of the esophagus should increase symptoms instead of providing complete comfort for the majority of patients in whom stricture has not occurred, and adequate relief by occasional passage of sounds for those in whom scar tissue has narrowed the lumen of the esophagus.

The dull burning type of substernal pain associated with sliding hiatal hernia frequently persists in spite of therapy.

WALLACE SPIGEL

SEVERE PULMONARY DISEASE SUBSEQUENT TO ZENKER'S DIVERTICULUM: Lloyd E. Hawes and James H. Walker. New England J. Med. 253:209 (11 Aug.), 1955.

Lipoid and suppurative pneumonia arising from ingestion of oils or cream is a well known clinical entity. Its occurrence in patients with esophageal disturbances (achalasia, scleroderma, benign and malignant strictures, traumatic or malignant perforations and diverticula) is quite common. The pulmonary lesions may be single, resembling lung tumor, or multiple, resembling tuberculosis, or abscess formation. Two cases are presented with Zenker's diverticula in which suppurative and lipoid pneumonia resulted from spillage of material from the high esophageal diverticula into the trachea. Lobectomy performed in both cases was hampered by large amounts of secretion that continued to spill into the trachea during and after the operation. In one case convalescence could not be accomplished until the diverticulum was inverted and later removed. In the second case a large Zenker diverticulum was not

looked for, nor recognized as the cause of the patient's pulmonary disease, until it was too late to remove it or to treat the resultant extensive suppurative pneumonia.

In conclusion, it is urged that before surgery is undertaken for a pulmonary lesion of unknown etiology, the presence of primary esophageal disease should be ruled out by barium fluoroscopy.

A. J. BRENNER

GASTRIC MUCOSA WITHIN THE ESOPHAGUS: Kenneth N. Morris. Australian & New Zealand J. Surg. 25:24-30 (Aug.), 1955.

The author calls attention to the presence of gastric mucosa within the esophagus. There is a clinical state in which the lower end of the esophagus is lined by gastric epithelium. The origin of this gastric mucosa is a matter of conjecture. It may be complicated by the development of reflux esophagitis and high esophageal stricture or by the formation of typical peptic ulcers which may hemorrhage, perforate or stenose. The correct line of treatment for this condition is a matter of debate but conservative therapy has been quite gratifying to this author.

BERNARD J. FICARRA

NEW METHOD FOR LOCAL ANESTHESIA IN PERORAL ENDOSCOPY: Hubert J. Adler. J.A.M.A. 159:111 (10 Sept.), 1955.

The author in order to avoid: 1. the toxic results of effective surface anesthetics, 2. discomfort to the patient caused by peroral endoscopy and 3. to achieve relaxation of structures underlying the mucosa of the pharynx and larynx has devised a new anesthetic procedure. It consists of injecting the superior laryngeal nerve with a procaine-hyaluronidase mixture. This is followed by injection of the greater palatine canal. Injection three is into the incisive fossae above the upper incisor teeth. The glossopharyngeal nerve is injected next and where necessary a fifth injection is made into the lingual tonsils. Injection six catches the pharyngeal root of the superior laryngeal nerve and injection seven is made into the posterior wall of the hypopharynx for help in esophagoscopies.

The above method is described as a safe and complete (deep) anesthesia, the entire procedure taking about 12 minutes.

WM. K. BILLINGSLEY, JR.

THE CONCEPT OF SPHINCTER SUBSTITUTION BY AN INTERPOSED JEJUNAL SEGMENT FOR ANATOMIC AND PHYSIOLOGIC ABNORMALITIES AT THE ESOPHAGOGASTRIC JUNCTION: K. Alvin Merendino and David H. Dillard. Ann. Surg. 142:486-509 (Sept.), 1955.

The authors discuss reflux esophagitis, cardiospasm and esophageal varices. Using 30 dogs, they interposed a segment of jejunum between the intact stomach and esophagus. Daily injections of histamine to produce a constant hyperacidity were given. The animals either died of perforation of stomach or duodenum or were sacrificed, and all specimens were sectioned. There were no ulcers of the esophagus in any of the animals. Several gastric and duodenal ulcers were present in all animals.

Utilizing an interposed jejunal segment based on the principle of spatial separation and contact of the esophageal mucosa from gastric secretion, they operated on 12 patients. There was one death. All patients were benefited markedly. The authors feel the clinical results to date have been so encouraging, that this operation has become standard procedure for some diseases unsatisfactorily treated in the past.

PAUL MATLIN

STOMACH

MULTIPLE BENIGN CHRONIC GASTRIC ULCERS: Thomas A. Johnson and Herbert L. Hawthorne. New England J. Med. 253:363 (1 Sept.), 1955.

Two cases of multiple benign gastric ulcers are reported in detail, with x-ray evidence before surgery of the presence of three ulcers in the stomach, one showing

the ulceration on the greater curvature in the antral portion of the stomach. The laboratory, history, and clinical workup all had shown evidence of a gastric ulcer. The literature is then reviewed, and many cases showing multiple ulceration are given, but very few of the many cases did show three gastric ulcers (especially on the greater curvature). The two cases had subtotal gastric resections. The patients had an uncomplicated recovery.

JOHN N. DILL

EOSINOPHILIC GASTRODUODENITIS WITH PYLORIC OBSTRUCTION: William S. McCune, Milton Gusak and William Newman. Ann. Surg. 142:510-518 (Sept.), 1955.

The authors discuss eosinophilic gastroduodenitis with pyloric obstruction. The sparse literature is reviewed, the majority of which cases had pyloric obstruction as the predominant symptom. All of the cases had high eosinophilic counts, ranging from 5 to 63 per cent. The specimens revealed generalized eosinophilic gastroduodenitis most marked in the antrum and prepyloric region.

The authors add three cases to the literature with no variations from the above picture of obstruction, eosinophilia and eosinophilic gastroduodenitis.

PAUL MATLIN

ON THE LATE RESULTS OF 435 CASES OF ORDINARY GASTRIC RESECTION FOR CANCER, WITH SPECIAL REFERENCE TO THE RELATION BETWEEN THE RESULTS AND THE HISTOPATHOLOGIC FINDINGS: Junichi Katami. Tohoku J. Exper. Med. 62:117 (25 Sept.), 1955.

This is a follow-up of 435 cases.

The author's discussion can only be followed and understood if the reader knows Petersen's (1904) classification of Cancer Histology and Borrmann's (1926) clinical staging. The findings and conclusions do not differ materially from any other similar study.

IRVIN DEUTSCH

RARE MALIGNANT TRANSFORMATION OF GASTRIC PEPTIC ULCER: E. Delannoy, M. Verhaeghe, A. Clay, J. Devambez and R. Knockaert. Ann. de chir. 31:527-538, 1955.

The authors call attention to statistical contradictions concerning the frequency of malignant transformation of Cruveilhier's gastric benign ulcer.

They point out that only the histological findings are of some value, and even then it is necessary to work from many specimens in order not to mistake a limited zone of malignant transformation (error by omission) and that the neoplastic nodule does not exist but in a limited point of the ulcer with its own histologic characteristic. It is also possible that the primitive cancer has been almost completely destroyed by the peptic digestion leaving in the specimen but a limited zone of malignant structure. Finally, in very extended carcinomas, the proof of degeneration cannot be really considered. It only can be hypothesis or probability.

Under these conditions of study, the authors have found in 308 gastrectomies studied—over a 10-year period—from the clinical, x-ray and histological points of view—only 3 malignant transformations of ulcers, against 62 cancers and 243 benign ulcers.

In summary, only the confused terminology permits consideration of malignant transformation of benign ulcer to be frequent (10 to 20 per cent for certain authors). In fact it is rare and for these authors does not exceed 1 per cent.

Eight cases are reported.

GUY ALBOT

INTESTINES

DIVERTICULITIS OF THE CECUM: T. S. BOOZER. J.M.A. Alabama 25:33 (Aug.), 1955.

A review of the literature and a summary of seven cases of diverticulitis of the cecum seen on the surgical service of St. Margaret's Hospital, Montgomery, Ala. is

presented by Boozer. Five hundred sixty-two barium enemas done at the same hospital between 1950 and 1954 are also reviewed and revealed diverticuli of the cecum in 1.8 per cent of the patients examined, corresponding closely to the percentage incidence found elsewhere. Age distribution in the cases reported ranged from 18 to 53 years with a predominance of males in ratio of 2¼ to 1. All of the cases were thought to have had acute appendicitis preoperatively except one case in which the appendix had been previously removed. Acute appendicitis and carcinoma of the cecum are the two most important lesions to be considered in differential diagnosis. Vomiting was present in only two of the author's cases, nausea in three. The author's impression was that patients with acute cecal diverticulitis did not appear as ill on admission as those with acute suppurative appendicitis. The treatment of choice is the simplest operative procedure which will adequately deal with the situation at hand.

JOHN M. MCMAHON

POSTOPERATIVE RECURRENCE OF CANCER OF COLON DUE TO DESQUAMATED MALIGNANT CELLS: Alfred A. Pomeranz and John H. Garlock. J.A.M.A. 158:1434 (Aug.) 20, 1955.

In a study of 20 unselected cases of carcinoma of the colon coming to surgery, the authors attempt to establish the relative importance of cancer cells disseminated during operation as a cause of postoperative recurrence. The study was instituted largely as the result of the suspicion by one of the authors (J.H.G.) that viable malignant cells can be rubbed off the serosal aspect of colonic neoplasms during operative manipulation not only by relatively rough gauze pads and sponges but also by the surgeon's gloves.

By the use of glass slide smears taken from the serosal aspect of the tumor and the gentle rubbing of sterile cotton tipped applicators across tumor surfaces the authors were able to recover unmistakable neoplastic cells in 10 per cent (2) of the cases. Thus it was apparent that cancer cells rubbed off tumor surfaces during operative manipulations must constitute a grave danger to dissemination and implantation within the peritoneal cavity.

In an effort to obviate these possibilities of dissemination, the authors designed a colon cover modified from ordinary gauze abdominal pads. Of sufficient capacity to surround the tumor bearing portion of colon this device also combines occlusive ligatures at a distance from the tumor as recommended by McGraw and associates.

WM. K. BILLINGSLEY, JR.

THE SIGMOIDOSCOPIC APPEARANCE OF THE INTESTINE IN HEALTH AND DISEASE: Ryle A. Radke. Military Med. 117:108 (Aug.), 1955.

The author describes the appearance of the normal rectal mucosa with the variations which often occur. Diffuse granularity is thought to be a normal phenomenon. The term "diastolic red" is used to describe the appearance of the intestine which is associated with elevation of the diastolic blood pressure. Emotional tension is characterized by bright red spots beneath normal mucosa, while antibiotics often cause a red roughened mucosa more intense than that caused by emotional tension.

In the diseased intestine factitious proctitis is described as the most often encountered deviation from the normal and is caused by trauma from an enema tip, sigmoidoscope or the rectal installation of irritating substances.

He describes the picture seen in amebiasis from superficial erosion to scarring and believes that miliary abscesses are characteristic of amebiasis.

The picture seen in chronic ulcerative colitis (thrombro-ulcerative colitis), schistosomiasis, adenomatous polyps and carcinoma is described with accompanying illustrations.

ZACH R. MORGAN

STUDIES OF ULCERATIVE COLITIS. III. THE NATURE OF THE PSYCHOLOGIC PROCESSES: George L. Engle. Am. J. Med., 19:231-256, 1955.

Engle reviews the available data concerning psychologic processes in ulcerative colitis summarizing published reports on more than 700 patients as well as his own

observations in 39 cases. Defects in personality structure long antedating the onset of colitis, a characteristic type of dependent and restricted relationship with people, consistent psychopathology in the mothers, and failure to achieve full heterosexual development was found in these patients with impressive consistency. The onset and relapses of the disease were found to occur in settings which represented to the patient real, threatened or fantasied interruptions of key relationships, but the disease developed only when the corresponding affect was one of helplessness, despair, hopelessness or depression. In conflict situations such affect was not noted, other neurotic, psychotic psychosomatic reactions were observed, especially headache. All of the various psychosomatic hypotheses are critically reviewed and a modified formulation is offered by the author which stresses the significance of the mother child symbiosis in determining the particular personality development and vulnerability to separation. The tissue reaction of ulcerative colitis is related to biologic changes occurring consequent to traumatic separations. Engle attempts to account for the choice of organs, namely, the colon, on the basis of constitutional and experimental factors in the mother-child transaction.

This is the third in Dr. Engle's series and, in the opinion of the reviewer, all are "must" readings for those interested in ulcerative colitis.

JOHN M. MCMAHON

CANCER APPEARING IN A PATIENT SUFFERING FROM HEMORRHAGIC RECTOCOLITIS: Hillemand, Verne, Leboue and Faibre. Arch. mal. app. dig., 44:577, (May), 1955.

The authors have taken up the study of the relationship between the two diseases and stress the discrepancy between European and American statistics. While in France cancerization is considered exceptional (1 per cent), in America it is considered much more frequent.

Most American writers consider that rectocolitis is complicated by polyposes and that the polyposes degenerate.

In the opinion of the authors, during hemorrhagic rectocolitis there exist polyposes which never degenerate, while the adenoma frequently degenerates, and they query whether American observations of rectocolitis with polyposes complicated by cancer do not rather concern diffuse rectocolic polyposes and not hemorrhagic rectocolites.

CECAL FORMS OF CROHN'S DISEASE: R. Vigure and F. Eudel. Arch. mal. app. dig., 44:598, (May), 1955.

The history, clinical examination, family antecedents and radiographies of this 26-year old woman confirmed cecal tuberculosis. The disease proved resistant to medical treatment. A hemicolectomy on the right side was performed in one phase. Several anatomopathologists who were consulted definitely ruled out tuberculosis; they thought Crohn's disease more likely. Forty days after surgery, a pyostercoral fistula appeared and persisted despite treatment. After four months, a further operation was performed to remove extensively with the first anastomosis, which was healthy, a terminal small intestine which was obviously very diseased. The histologists were emphatic about it: a typical attack of acute ileitis.

Three points should be stressed: 1. the extreme rarity of this purely cecal form. 2. the very early relapse: 40 days after the first operation, 3. the cure, a year later, after a further operation, due to an exeresis over a very wide area and extensive infiltration of the mesos by novocaine.

CLINICAL AND THERAPEUTIC REFLECTIONS CONCERNING 50 CASES OF CANCER OF THE RIGHT COLON: R. Peycelon and G. Guillemin. Arch. mal. app. dig., 44:877, (July), 1955.

These are complete statistics of cancer of the right colon including all the cases observed by the authors without any selection.

The clinical manifestations were quite variable and very indistinct. Furthermore most of the patients were seen late.

Radiography has always verified the existence of the lesion.

The radical operation by hemicolectomy of the right colon was performed on 33 patients out of 50, and palliative operations on 17.

Mortality was 14 per cent for cold operations, 60 per cent for operations for acute occlusion.

Seventeen long-term results reveal survivals of from 1 to 21 years.

GUY ALBOT

ACUTE AND SUBACUTE TERMINAL ILEITIS: Mm. Cherigie, Tavernier, Dupas and Mrs. Raynal. Arch. mal. app. dig., 44:205, (6 July), 1955.

In our department at the Claude Bernard Hospital, we had the opportunity to study hundreds of patients, children and adults, showing pseudoappendicitis or appendicular points which appeared in the course of infectious diseases (scarlet fever, angina, pneumonia, measles) or parasitic diseases.

Other inflammatory infections (tuberculosis, Crohn's disease, typhoid fever) also begin with lymphoid hypertrophy of the small intestine. Finally, the primitive mesenteric adenitis and the inflammatory follicular hypertrophy seem to us to be one and the same affection.

It is our theory that most infectious diseases, including typhoid fever, Crohn's disease and so on . . . often begin with a follicular ileitis that can be more easily discovered in the last part of the ileum. However, we found similar hypertrophy on the other parts of the small intestine and on the colon.

DISEASE OF THE TERMINAL PORTION OF THE COLON: John R. Hill. J. Indiana M. A., 48:857, (Aug.), 1955.

About 12 per cent of all malignant conditions of the human body originate in the anus, rectum or lower portion of the sigmoid colon. The most common tumor arising in this area is the adenomatous polyp; 10 per cent of persons more than 40 years old have been found in various detection centers to have one or more adenomatous polyps in the lower 10 inches of the bowel. Detection is facilitated by the fact that 70 per cent of all adenomatous polyps and malignant lesions of the colon can be reached with a 10-inch sigmoidoscope.

Carcinomas and polyps are frequently associated and a diligent search for carcinoma should be conducted whenever a polyp is found by sigmoidoscopic examination. This necessitates careful radiographic examination of the entire large bowel. Frequently polyps are multiple but the fact that a patient has multiple adenomas does not necessarily mean that familial polyposis is present. The author has seen 25 to 30 polyps in the lowest 10 inches of the bowel, yet repeated radiographic examinations of the colon were negative. Preferred treatment is colectomy and ileosigmoidostomy.

Epitheliomas of the anus have a high grade of malignancy and prognosis is poor. The best treatment is combined abdominoperineal resection plus radical resection of the inguinal lymph nodes.

Diagnosis of basal cell epithelioma is possible only by biopsy. Adequate treatment consists of wide local excision.

Submucosal nodules of the rectum may be oleomas, residuals of inflammatory lesions, or benign neoplasms. The most commonly encountered benign neoplasms are leiomyomas, lipomas and lymphomas while lymphosarcomas, leiomyosarcomas and carcinoids are the most frequent malignant ones.

All carcinoids are potentially malignant. The author's experience indicates that minute carcinoids of a few millimeters in diameter can be removed safely by local excision, while those with more than 1 cm. in diameter and those that are invasive must be treated radically.

JOSEPH E. WALTHER

PATHOLOGIC EVALUATION OF RECTAL LESIONS: Oscar B. Hunter, Jr. Am. J. Proct., 6:301, (Aug.), 1955.

The author very clearly describes the value of a very complete pathologic study and report of rectal tissues to help the surgeon better manage his patient therapeutically, palliatively, and prognostically. The commonest lesions encountered are polyps, and carcinoma. He stresses a careful gross description of the lesions, size, color, etc., associated tissues, and lymph nodes.

Polyp study must indicate tissue changes on the tip, and presence or absence of stalk invasion of malignant changes. Segmental resections are indicated if stalk invasion reaches the bowel wall, and where surface changes are found on sessile polyps.

Confirmation of malignancy of tissue is not sufficient for the surgeon. He must know the grade of lesion. Duke's classification is most helpful, along with the evidence of lymph channel, lymph node, and vascular invasion.

HERMAN MILLER

ANORECTAL AND COLON DISEASE: Louis E. Moon. J. Omaha Mid-West Clin. Soc., 16:61, (Aug.), 1955.

A panel discussion on anorectal and colon disease was opened by the author's discussion of bizarre symptoms and manifestations. Urinary frequency unaccounted for, was relieved by removing chronically prolapsed hemorrhoids. Toxic labyrinthitis and toxic optic neuritis were cleared up after correcting the colon disease present. Patients with ulcer symptoms, arthritis, and asthma, in many instances were relieved of symptoms following anorectal surgery.

Conversely, bowel symptoms may be secondary to other diseases. Rectal bleeding frequently arises from the upper gastrointestinal tract. One patient with bowel obstruction was relieved by emptying a distended bladder. Paralytic ileus may be caused by ureteral obstruction.

In conclusion, three rarities are cited. A transverse colon carcinoma was biopsied low in the rectum; a polypoid mass, prolapsed and replaced, could not be visualized on proctoscopy; and a positive Virchow node from a rectal carcinoma.

NORMAN L. FREUND

ANORECTAL AND COLON DISEASE SYMPTOMS LEADING TO ERRONEOUS DIAGNOSES: Arthur M. Greene. J. Omaha Mid-West Clin. Soc., 16:62, (Aug.), 1955.

The diseased colon, aside from the usual well known symptoms, may center our attention away from the primary cause to some other site. Cardiopulmonary disease is often suspected in cases of gaseous distention and spasm of the splenic flexure. Proof of diagnosis is made by a history of relief of chest pain following passage of flatus or bowel movement. Upper abdominal complaints referable to the gallbladder frequently arise from lower bowel obstruction due to adhesions, constipation or anal stenosis. Arthralgia, *erythema nodosum*, episcleritis and iridocyclitis are complications of chronic ulcerative colitis. If the disease is limited to the right side, the etiologic factor can easily be missed.

The author concludes with erroneous diagnoses of the lower bowel itself, made in the face of anorectal disease, such as regional enteritis causing anal fistulae, and a carcinoma lying above large hemorrhoids. Obstruction of the left colon usually causes pain and perforation of the thinnest piece of bowel, the cecum, and may be caused by a lesion that even at operation cannot be differentiated between carcinoma and diverticulitis.

NORMAN L. FREUND

ANORECTAL AND COLON DISEASE FROM THE STANDPOINT OF THE PATHOLOGIST: Horace K. Giffen. J. Omaha Mid-West Clin. Soc., 16:65, (Aug.), 1955.

The cecum is a catch basin with relative stasis, therefore subject to chronic infections such as amebiasis, terminal ileitis and oxyuriasis, and also the site of intussusception. The author discusses chronic ulcerative colitis and reviews the observa-

tion from the Mayo Clinic that the myenteric plexus ganglia were more numerous than normal, but could not verify this finding. Also mentioned briefly is diverticulitis, uremic colitis, and heavy metal poisoning.

Melanosis coli is ascribed to stasis and repeated hemorrhage (an etiologic factor in disagreement with that generally accepted, i.e. due to anthracene laxatives). Benign and malignant tumors are discussed.

Exfoliative cytology is an inadequate means of diagnosis of colon tumors. Biopsies are satisfactory, but should be from the edge of the lesion, be it mass or ulcer, and should be obtained by a skilled surgeon, for small fragments are inadequate.

NORMAN L. FREUND

URINARY MANIFESTATIONS OF COLON, RECTAL AND ANAL DISEASE: Henry Kammandel. J. Omaha Mid-West Clin. Soc., 16:68, (Aug.), 1955.

Close anatomic relationship and mutual neurogenic innervation allows disease of one organ to affect another. Colon disease affects the urinary tract more often than the reverse. The kidney may be involved by direct extension of neoplasms or diverticulitis, but is rare.

Involvement of the ureters from the rectosigmoid is common in males, and also in females following hysterectomy. Diverticulitis causes hydroureter and hydronephrosis. Tumors by direct extension also cause obstruction of urine, but less commonly. This back pressure may not cause obvious symptoms, so that a complete urologic examination is indicated prior to colon surgery, to evaluate procedure and prognosis.

Bladder infection demands cystoscopy, and if a granulating area is noted posteriorly, proctoscopy and barium enema x-ray are indicated to rule out diverticulitis with colovesical fistula. Urinary morbidity after proctosigmoidectomy is 100 per cent. Indwelling catheter is required for 7-10 days in all cases, with resultant secondary infection. Exaggeration of a prior stricture or prostatic obstruction is often overlooked but the cause for retention in most patients is unknown. Persistence of obstruction in 60 per cent of males and 40 per cent of females is a most important urologic problem secondary to this operation.

Differentiation of prostatic from rectal carcinoma by digital examination should be easy. The fascia of Denonvillier acts as a barrier to prostatic tumors, but the opposite is not true. Perirectal extension from the prostate may cause some errors, but the mucosa in these cases is always normal.

Hemorrhoids, constipation and hernia in the elderly male may be caused by straining due to obstructive uropathy. Ischiorectal infection can cause urethral symptoms of frequency, decreased stream or retention. Extension below Colle's fascia accounts for inflammatory or neoplastic spread to the shaft of the penis and lower abdominal wall.

NORMAN L. FREUND

URINARY MANIFESTATIONS OF COLON, RECTAL AND ANAL DISEASE FROM THE STANDPOINT OF THE RADIOLOGIST: Francis L. Simonds. J. Omaha Mid-West Clin. Soc., 16:72, (Aug.), 1955.

Colon x-ray studies must include filling the entire large bowel with barium under fluoroscopic examination. The flexures are visualized by rotating the patient, and spot films taken of any suspicious area. Double contrast studies should be routine. To avoid overfilling, the barium is run into the splenic flexure only, and the patient turned on his right side, filling the rest of the colon by gravity.

Inadequate preparation is the most frequent cause of failure. The author uses a strong cathartic the night before, and a cleansing enema in the morning.

Errors of interpretation are due to the inexperience of the observer, inadequate preparation, attempts to diagnose low rectal lesions (instead of by proctoscopy), and deformities due to spasm.

NORMAN L. FREUND

URINARY MANIFESTATIONS OF COLON, RECTAL AND ANAL DISEASE—SURGICAL MANAGEMENT: Julius B. Christensen. J. Omaha Mid-West Clin. Soc., 16:75, (Aug.), 1955.

The author discusses chronic anal fissure with fibrosis. Surgical correction is necessary and the circular scar tissue must be incised, for dilatation only causes fur-

ther fibrosis. A sliding graft from the posterior perianal skin offers the extra tissue needed, that is in itself elastic in nature, has a good blood supply, and can be performed without tension. The results are excellent.

NORMAN L. FREUND

BOWEL FUNCTION AFTER COLECTOMY FOR CANCER, POLYPS AND DIVERTICULITIS: Richard C. Lillehei and Owen H. Wangensteen. J.A.M.A., 159:163, (17 Sept.), 1955.

This is a very thought-provoking study which has as its tenet that total or subtotal colectomy should become under favorable circumstances the operation of choice for cancers of the colon beyond the hepatic flexure. This is supported by the increasing evidence compiled by the authors and others that when total or subtotal colectomy is done for polyps or carcinoma of the colon, an appreciable number of concealed lesions are uncovered, remote from the site of the primary lesion for which the operation was indicated. Thirty-eight per cent of the cases in this study were found to have additional polyps in an area of the colon believed to be uninvolved preoperatively. In this same group of patients 18 per cent developed, either simultaneously or successively, in time a second carcinoma of the colon.

It was found that prolonged postoperative diarrhea did not occur where coincident resection of terminal ileum could be kept below 30 cm. of ileum removed. Also where the ileocecal valve could be preserved, diarrhea rarely persisted.

The "second look" procedure is discussed and devices to improve accomplishment in colic cancer are suggested.

WM. K. BILLINGSLEY, JR.

LIVER AND BILIARY TRACT

PREVALENCE AND NATURE OF HEPATIC DISTURBANCE FOLLOWING ACUTE VIRAL HEPATITIS WITH JAUNDICE: John R. Neefe, Joseph M. Gambescia, Charles H. Kurtz, Hugo Dunlap Smith, Gilbert W. Beebe, Seymour Jablon, John G. Reinfold and S. Clay Williams. Ann. Int. Med. 43:1 (July), 1955.

This paper concerns a follow-up study of 651 patients who had had acute viral hepatitis in the army, or who had "heavy exposure" to hepatitis, as against controls who had "minimal" exposure.

The BSP retention test, zinc turbidity and A/G ratio of all the laboratory tests were in best agreement with the history and physical examination. It was interesting to note that two to five per cent of apparently healthy persons who gave no history of hepatic disturbance showed signs of abnormal laboratory liver function tests. The most important tests for screening purpose were the BSP retention test and the 24-hour urine urobilinogen excretion test.

There was no significant statistical association of hepatic disturbance with a prior history of hepatitis. Liver biopsies tended to show nonsuspected causes for abnormal liver function tests in those patients with a prior history of hepatitis. Thus, the presence of a hepatic disturbance in a person with a previous history of viral hepatitis does not necessarily afford evidence of causal relationship, especially if it occurs more than three symptom-free years following an initial attack of hepatitis. There was no case in this series with advanced chronic hepatic disease that could be attributed only to the preceding viral hepatitis, and other factors in addition to, or other than, the hepatitis were found to be necessary to cause a chronic liver condition.

STANLEY STARK

JAUNDICE AFTER DISCONTINUANCE OF CHLORPROMAZINE: Gerald C. Kohl, Frank R. Maddison and Richard E. Davis. Northwest Med. 7:716 (July), 1955.

The importance of differentiating chlorpromazine jaundice from a surgically correctable jaundice is discussed. A case is reported where jaundice due to chlorpromazine developed five days after the drug had been discontinued. Reports in the lit-

erature vary widely as to the reported incidence of chlorpromazine jaundice, and only four other cases of delayed jaundice have been mentioned. Reports are also mentioned concerning the possible duration and toxicity of chlorpromazine jaundice. Some criteria which may aid in making the diagnosis are given: 1. a high index of suspicion, 2. current, or previous, administration of chlorpromazine, 3. laboratory findings suggestive of an obstructive type of jaundice, and 4. a transient peripheral eosinophilia, although this has not always been reported.

ARNOLD L. BERGER

THE PRACTICAL CONSIDERATIONS IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE: I. I. Cash. Wisconsin M. J. 54:340 (July), 1955.

Abnormal liver function tests do not make a diagnosis, and structural changes in the liver are not measurable with any degree of accuracy in terms of abnormal function. The oral use of antibiotics may act somehow to curb the bacterial reduction of bilirubin to urobilinogen, all of which makes a differential diagnosis by means of laboratory tests very difficult.

With these salient findings in mind, the author has attempted to indicate which examinations are of value in the differential diagnosis of jaundice. The article includes a number of tables which may be of help in expediting the intelligent use of *available* laboratory procedures. He points out, and correctly, that examinations such as serum bilirubin and icterus index are not tests of liver function; they measure only the amount of interference with the enterohepatic circulation of bile. They do not tell where the interference is.

"It must first be clearly understood that a well-taken history and a skillfully performed physical examination can make a correct diagnosis in at least 80 per cent of jaundiced patients".

IRVIN DEUTSCH

HEPATIC NECROSIS AND OTHER VISCERAL LESIONS ASSOCIATED WITH PHENYLBUTAZONE THERAPY: Joan M. MacCarthy and R. T. Jackson. Brit. M. J. 4933:240 (23 July), 1955.

The authors present a single case of death due to Phenylbutazone therapy and attempt to ascertain the etiology of the multiple pathological findings on autopsy. They claim the hepatic and renal necrosis are due to the toxic action of Phenylbutazone, while the myocarditis is due to a sensitivity to the drug. Alteration in the appearance of the granulomata associated with the rheumatoid lesions is thought to be due to the effect of the drugs used in therapy.

ABE ALPER

TOXIC NEPHROSIS AND MASSIVE HEPATIC NECROSIS PRODUCED BY URETHAN: John F. Flanagan. A.M.A. Arch. Int. Med. 96:277 (Aug.), 1955.

Prolonged urethan administration represents the current treatment of multiple myeloma. Gastrointestinal irritation and suppression of the formed blood elements may be caused by such therapy. Occasionally, massive hepatic necrosis may occur. The case of a 39-year old male patient is reported who was suffering from multiple myeloma and who developed, after taking 2 to 4 gm. of urethan daily over a period of 10½ months, a sudden severe hematemasis. This was followed by jaundice, hepatic failure, coma and death. Autopsy showed extensive centrilobar and midzonal necrosis of the liver. There were also hemorrhages but little inflammatory cell infiltration. In addition, the autopsy revealed a moderate ascites, hemorrhagic erosions of the stomach and an unusual form of tubular nephrosis which must be attributed to urethan toxicity as it showed neither the features of cholemic nor of myeloma kidneys.

H. B. EISENSTADT

TRANSHEPATIC VENOUS CATHETERIZATION AND VENOGRAPHY: Howard R. Bierman, Keith H. Kelly, Laurens P. White, Alexander Coblentz and Arthur Fisher, J.A.M.A. 158:1331 (13 Aug.), 1955.

By virtue of a relatively simple percutaneous method of transhepatic portal venipuncture the authors have performed venipunctures successfully in all but nine

of 73 patients attempted. Fourteen patients were catheterized via the portal or hepatic venipuncture needle and the tubing left in place for 2 to 19 days without sequelae. In 3 patients both the hepatic and the portal veins were catheterized by the transhepatic approach without untoward reaction. Venograms were obtained in all patients to confirm the position of the needle or catheter.

Studies made possible by this method included hydrostatic pressure within the portal vein and relative oxygen, protein, urea, sodium, potassium, chloride, calcium or phosphorus content of the portal blood compared with that of arterial or hepatic venous blood or venous blood taken elsewhere. It was also possible with use of the venogram to suggest the presence of neoplastic involvement of the liver through distortions of the venous pattern. Hepatic arteriograms and portal venograms in the same patient on five occasions permitted accurate comparisons between the arterial and portal venous supply of the liver.

Postmortem examinations on patients previously studied revealed no serious hemorrhages or extravasations. The authors conclude that their experience with this technic over the past 2 years indicated that portal venipuncture may be employed safely as a valuable clinical and investigative aid.

WM. K. BILLINGSLEY, JR.

EFFECTIVENESS AND COMPLICATIONS OF NEEDLE BIOPSY OF THE LIVER: Dennis A. J. Morey, Robert Means and Kemp Plummer. J.A.M.A. 158:1489 (27 Aug.), 1955.

From a total of 139 liver biopsies carried out at the Richmond Veterans Administration Hospital, 19 biopsies failed to reveal the diagnosis finally established (13.8 per cent). As might be expected metastatic carcinomas accounted for over 50 per cent of the failures. Four biopsies failed to show a histological picture of portal cirrhosis (4.6 per cent).

Hemorrhage was the only severe complication occurring in four cases with one death. In 3 of these 4 cases prothrombin times had been less than 40 per cent. In each case Vitamin K had been administered with transient restoration of prothrombin time to above 60 per cent. In retrospect the authors suggest that a prothrombin consumption time be done to further rule out potential bleeders and that Vitamin K be given postoperatively until all danger of hemorrhage is past.

WM. K. BILLINGSLEY, JR.

VISUALIZATION OF BILIARY DUCTS BY INTRAVENOUS INJECTION OF NEW CONTRAST MEDIUM: Alexander J. Link, Raj K. Parida, Julius Heydemann and Robert M. Kark. J.A.M.A. 158:1491 (27 Aug.), 1955.

Sodium Iodipanide (cholografin) was injected intravenously in 21 cases in a study to determine its efficacy in visualizing biliary ducts under various clinical circumstances. Adequate visualization was obtained in 15 of the 21 cases. The six cases failing to visualize had either severe liver disease or air in the ducts following surgery. No serious reactions developed following slow injection of the compound. Serial liver function tests confirmed the low toxicity of the preparation.

WM. K. BILLINGSLEY, JR.

FEASIBILITY OF PARTIAL HEPATIC RESECTION UNDER HYPOTHERMIA: William F. Bernhard, James D. McMurrey and George W. Curtis. New England J. Med. 253:159 (4 Aug.), 1955.

An investigation on dogs was carried out to determine the effect of hypothermia on liver parenchyma alone and the effect of vascular occlusion on that organ during hypothermia.

Histologic study of the liver and postoperative liver function tests in dogs subjected to hypothermia were entirely negative.

In normothermic animals with afferent hepatic vascular occlusion for one hour the mortality was 100 per cent. Preoperative administration of antibiotics did not alter this result.

Under hypothermia vascular occlusion of the hepatic afferent artery for one hour was carried out successfully, with only 2 deaths in 27 dogs. There were no deaths in the

last 20 consecutive dogs in this series. No antibiotics were administered.

Liver resection is feasible with a dry field utilizing afferent vascular occlusion hypothermia.

It is suggested that the surgical indications for use of hypothermia be extended to include patients with hepatocellular disease requiring anesthesia and surgery, patients with primary or secondary tumors of the liver who might be successfully treated by liver resection and patients with tumor extension to the portal vein who might not otherwise be considered capable of surviving operation.

Hypothermia appears to be superior to hypotensive technics as an adjunct to the anesthetic management of patients.

BERNARD STERN

AN EVALUATION OF THE SERUM IRON IN LIVER DISEASE: Chauncey M. Stone, Jr., John M. Rumball and Claire P. Hassett. Ann. Int. Med. 43:229 (Aug.), 1955.

The serum iron levels in 61 patients with liver disease are reported. The diagnosis was made by history, physical examination and laboratory studies. It was confirmed by liver biopsy in 56 of the patients. Serum iron was determined by a modification of the Barkin and Walker method. In 25 normal controls the serum iron ranged from 70 to 170 gamma per cent. In cirrhosis of the liver the mean was 102 gamma per cent, in obstructive jaundice of various causes, it was 116 gamma per cent and in acute hepatitis, it was 240 gamma per cent.

The conclusions reached from this study were that elevated serum iron levels are suggestive of hemosiderosis, hemochromatosis, acute viral hepatitis or diseases associated with hemolysis. Serum iron levels reach a peak in acute hepatitis from 12 to 31 days from the onset of the jaundice, and a late peak tends to indicate a more prolonged course. There is no relation between the serum bilirubin and the serum iron levels. It is suggested that the peak of the serum iron levels may coincide with the period of maximal hepatic necrosis.

It is believed that this test is very effective in distinguishing the causes of early jaundice and as such should be added to the battery of liver function studies.

STANLEY STARK

TUMORS OF THE EXTRAHEPATIC BILIARY TRACT: Jalin R. Steeper. J. Internat. Coll. Surg. 24:180-191 (Aug.), 1955.

A series of 35 tumors of the extrahepatic portion of the biliary tract is reported. These tumors both benign and malignant, were encountered in 4,180 operations on the biliary tract.

By far the most frequent was carcinoma of the gallbladder. The discouraging results in the treatment of this disease are pointed out by the author's statistics, which show an average survival time of three months for patients operated on. The rationale of "prophylactic" cholecystectomy is discussed.

The various types of benign tumor of the gallbladder and ducts are described. The literature is reviewed with respect to the occurrence, diagnosis and treatment of these lesions.

Malignant lesions of the bile duct are discussed. With the exception of ampullary tumors, these lesions present the same hopeless outlook as does carcinoma of the gallbladder.

Intravenous cholangiographic study is suggested as a means of earlier diagnosis of ductral tumors.

ABRAHAM BERNSTEIN

SURGICAL TREATMENT OF NONCALCULOUS BILIARY TRACT DISEASE: Daniel J. Preston. J.A.M.A. 159:17 (3 Sept.), 1955.

After reviewing the pitfalls of surgery in noncalculous cholecystitis, the author discusses methods for improving the results of treatment of noncalculous biliary tract disease.

Indication for surgery in the absence of demonstrable calculi is primarily a concise history of recurrent biliary colic and the author elaborates on significant clinical details. The differential diagnosis involved in biliary tract disease is well discussed.

Indications for exploration of the common duct include: 1. thickening, dilatation and opacity of the duct, 2. thickening edema

or nodular fibroses of the pancreas associated with a thickened or dilated common bile duct, 3. a thickened contracted gallbladder, 4. a cholesterolosis cholecystitis and 5. dilatation of the cystic duct. The author advocates probing of the duct via the ampulla of Vater through the supraduodenal approach.

The remainder of the article deals with surgical technics in dealing with operative eventualities. After retrograde exploration of the common duct ampulloduodenostomy is accomplished in a manner permitting a permanent enlarged opening at the choledochoduodenal junction. Thus continuous unimpaired postoperative internal drainage of bile and pancreatic juice is accomplished without a T-tube drain and recurrence of postoperative cicatricial stricture of the distal end of the common duct is prevented. Much immediate postoperative morbidity is avoided thereby.

WM. K. BILLINGSLEY, JR.

PATHOLOGY AND LABORATORY RESEARCH

THE PATHOGENESIS OF ACUTE PANCREATITIS: Henry Wapshaw. Glasgow M.J. 36:76 (Mar.), 1955.

Regardless of the chemicophysical mechanism, spontaneous activation of the pancreatic juice is fraught with potentially grave consequences. This is portrayed in cases in which prolonged exhibition of parasympatheticomimetics has resulted in hyperacute pancreatitis. For example, Mecholyl, taken in this manner tends to produce focal hemorrhages in the pancreas which has been known to be associated with vacuolization of the acinar cells and fat necrosis.

It is also well known that the most widespread pathology ensues when the pancreatic ducts are invalidated during or preceding active pancreatic secretory activity. The author employed morphine as an active obstructive agent in actively secreting glands in which not more than a four hour obstruction was produced. In spite of this, a profound disturbance, comparable with that of acute pancreatitis, was noted in the serum enzyme concentration. An additional factor lies in the tendency to pancreatic autodigestion in the presence of anemia due to circulatory deficiency. The effect of ischemia is that of stimulating the conversion of trypsinogen into active trypsin. The similarity between obliteration of the external pancreatic ducts and the pathology of acute pancreatitis is striking. This entity is increasingly being considered as a separate and distinct condition and not merely a stage of other diseases.

Surgical evidence of ligation of the pancreatic ducts, in the radical operation for treatment of neoplasms of the head of the gland, reveals that this procedure does not result in necrosis or even severe edema. The implication is that ductal obstruction is of relatively little moment in the etiology of acute pancreatitis.

The therapeutic trend, based on an etiology of vagotonia in acute pancreatitis, is that described by the authors. While there is an accumulation of evidence to support retention of protryptic enzymes during active hypersecretion, other coexisting or individual etiological factors must not be ignored. These include the possibility of the action of bile which may come in juxtaposition to pancreatic tissue; some vascular disturbance; and deficient tryptic inhibitor.

REGINALD B. WEILER

CURRENT VIEWS ON THE MECHANISMS OF INSULIN ACTION: William C. Stadie. Am. J. Med. 19:257 (Aug.), 1955.

This discussion of recent advances of the diabetic metabolism and the insulin action makes the following statements of interest: all fat mechanism goes through the formation of two carbon compounds. These condense with four carbon compounds to enter the Krebs cycle for further conversion or oxidation. The four carbon compounds necessary for combination with a two carbon compound always come from preexisting carbohydrates and never from fat. Hence a new formation of carbohydrates from fatty acids does not occur.

A pathway of metabolism of glucose other than through the glycolytic cycle exists by oxidation of hexosemonophosphate to phosphohexonic acid. This process does not involve insulin. The effect of insulin on

carbohydrate metabolism has been clarified by the use of radioisotopic glucose. Insulin increases the oxidation of glucose fourfold, glycogen storage fivefold, incorporation into protein sixfold and into fatty acids thirteenfold. In the absence of insulin, synthesis of glycogen by the liver and the muscles persists, but the rate of formation is diminished. The ability of the liver of the diabetic to synthesize fat is impaired. A large amount of fat is broken down in the liver to ketone bodies which are completely oxidized in the peripheral tissues and are therefore an important source of energy. This takes place in diabetic acidosis where only a small amount of ketones is excreted in the urine in comparison to the large quantity used in the body. Insulin increases fatty acid synthesis. Deficiency of fat metabolism is therefore a major defect of the diabetic. Fat synthesis fails due to the absence of intermediary substance derived from glucose. However, these substances can be furnished by fructose which the diabetic can metabolize properly. Therefore, there is only an indirect action of insulin on the fat metabolism. A similar indirect influence is also exerted on the protein metabolism. There are four theories on the action of insulin: 1. The permeability or transfer hypothesis suggests that insulin promotes the transfer of glucose into the cells. 2. The hexokinase theory assumes that insulin promotes the phosphorylation of glucose by glucohexokinase. 3. A third theory assumes an effect of insulin on the energy rich phosphate bonds. 4. A fourth one, on the oxidative reactions in the Krebs cycle.

H. B. Eisenstadt

NOCTURNAL GASTRIC SECRETIONS OF ULCER AND NONULCER PATIENTS UNDER STRESS: Peter Wolff and Jacob Levine. Psychosom. Med. 17:218 (May-June), 1955.

Ten male patients, five of whom had duodenal ulcers and five of whom were nonulcer cases, were chosen for the experiment.

In both groups the prestress values of gastric volume, free acidity, and total acidity were significantly different. In respect to the acidity, the ulcer group averaged two or three times as high as the other group. Before stress the curves for the ulcer patients exhibited typical high values in the early night period which dropped progressively until early morning readings were within normal limits. The tension release during sleep may account for this. The nonulcer group, highest levels were experienced at nightfall and also dropped during the sleeping hours. In contrast, however, to the ulcer group the extent of the drop was small.

Under stress, the reactions of the two groups differed. The nonulcer group showed a marked increase in secretion so that the curves now showed an early rise in acidity with a drop similar to the ulcer group but the values never reached the ulcer group levels under nonstress conditions. The value of secretion was much greater during stress than usual. On the other hand, no significant alterations took place in the ulcer group, so that no increase in secretion occurred in response to stress. It appears that these cases do not respond to mild stress in contrast to the nonulcer group. These differences are attributed to the fact that duodenal ulcer patients are laboring under persistent anxiety so that this gives rise to a chronic elevation of acidity. Perhaps a specific stimulus of a stressful nature peculiar to each patient might have given rise to still greater values but the mild and general type of the experimental stimulus failed to produce such a result. It is reasonable to conclude that the lack of response in these ulcer cases is due to the fact that additional external stress fails to produce further response in the secretory gastric mechanism because of a preexisting state of chronic tension-activity. The alarm mechanism is already present and acting continuously so that further alarm-responses do not provoke the same type of reaction that occurs in those patients free of a chronic alarm mechanism as far as the gastrointestinal system is concerned.

Reginald B. Weiler

BOOK REVIEWS FOR GASTROENTEROLOGISTS

LES CANCERS DU COLON (CANCER OF THE COLON): Marcel Roux, Assistant Professor, Faculty of Medicine of Paris and Surgeon of the Hospital and F. Carcassonne, Professor, Faculty of Medicine, Marseille, France, with collaboration of R. LeCannet, Chief of the Laboratory of the Faculty of Medicine, Paris, Radiologist of the Hospital of the Pasteur Institute, Paris, France, with a preface by Professor J. Seneque. 368 pages with 140 illustrations. Masson & Co., Paris, France, 1955. Price 2.600 fr.

A timely volume well written, printed and illustrated, dealing with cancer of the colon. The authors stress the diagnosis and other findings and discuss surgery, radiotherapy and other therapeutic meaures in the treatment.

An extensive bibliography and index complete the book. If translated into English, the reviewer believes that it would be well received by the surgeon.

SUPPLEMENT I—ATLAS OF EXFOLIATIVE CYTOLOGY: George N. Papanicolaou, M.D., Ph.D. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1956. Price $4.00.

The Atlas of Exfoliative Cytology by Dr. Papanicolaou was well received by the medical profession and this supplement is a welcome addition, which further enhances the study of smears obtained from the various organs. In this supplement, the physician will note that in addition to the smears, sections of the organs are also presented.

Physicians or pathologists who have not seen the original atlas should not hesitate to purchase it plus the 1956 supplement.

CURSO EXTRAORDINARIO DE CANCEROLOGIA PARA GRADUADOS ACTAS: Profesor Dr. Abel N. Canonico, Director, Instituto de Medicina Experimental, "Angel Rofto", Universidad de Buenos Aires, 1954, Director Honorario del Curso, Profesor Dr. George T. Pack.

This symposium was a graduate course dealing with cancer in all its phases and the participants included well known specialists from several countries, who aired their views pro and con. The reviewer regrets that summaries in English, French and German are not appended to the discussions which would enhance the value of this book.

A CIBA FOUNDATION SYMPOSIUM ON THE KIDNEY—ARRANGED JOINTLY WITH THE RENAL ASSOCIATION: Editor for the Renal Association—A. A. G. Lewis, M.D., B.S., B.Sc., M.R.C.P. Editor of the Ciba Foundation—G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. Assisted by: Joan Etherington. 335 pages, 125 illustrations. Little, Brown & Co., Boston, Mass., 1954. Price $6.75.

This very scientific volume dealing with the kidney is divided into five parts and embodies the proceedings of the Royal Society of Medicine, London, July 7th to 10th, 1953.

In reading this valuable contribution to medicine, the reviewer is amazed at the enormous data which appears between its covers. Page 15, the technic of renal biopsy, is discussed, its value in diagnosis in diffuse renal disorders, but of no value in focal ones, such as chronic pyelonephritis. The illustrations, Figs. 2, 3, 4 and 5, facing pages 20 and 21, demonstrate the histologic findings of the biopsy specimens.

Although the other parts of the monograph are also interesting, space does not permit a more comprehensive review. However, it is recommended that all physicians should read this highly scientific but interesting monograph dealing with the kidney.

HYPERTENSION—HUMORAL AND NEUROGENIC FACTORS: Editors for the Ciba Foundation—G. E. W. Wolstenholme, O.B.E., M.A., M.B. B.Ch. and Margaret Cameron, M.A., A.B., L.S. Assisted by: Joan Etherington. 294 pages, 73 illustrations. Little, Brown & Co., Boston, Mass., 1954. Price $6.75.

PERIPHERAL CIRCULATION IN MAN: Editors for the Ciba Foundation—G. E. W. Wolstenholme, O.B.E., M.A., M.B. B.Ch. and Jessie S. Freeman, M.B., B.S., D.P.H. Assisted by: Joan Etherington. 219 pages, 72 illustrations. Little, Brown & Co., Boston, Mass., 1954. Price $6.00.

Like the other volumes by the Ciba Foundation, Hypertension and Peripheral Circulation are highly scientific and deal with many interesting facts, some of which are unknown to many of us. It is recommended that physicians interested in knowing more about hypertension and disturbance of peripheral circulation should carefully peruse these monographs.

EL QUISTE HIDATICO DEL HIGADO ABIERTO EN LAS VIAS BILIARES—Tesis de Doctorado por el Dr. Muzio S. Marella. Facultad de Medicina de Montevideo, Uruguay, 1955.

A thesis for the doctorate in medicine as required by the faculty of medicine, University of Montevideo, written by Dr. Muzio S. Marella. The thesis deals with hydatid infestation of the liver and the various complications caused by the parasite. The illustrations and bibliography are excellent. The reviewer recommends that the author or the university summarize or reprint the entire thesis in one or more languages, so that it may be available to a larger group of readers.

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2. Morrison, Samuel: Am. J. Gastroenterology 22:309 (1954).
3. Rossett, N. E., Rice, M. L., Jr., Gastroenterology 26:490 (1954).

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